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PROBLEMS OF NOMENCLATURE OF CERTAIN PATHOGENIC RICKETTSIAE AND RICKETTSIAL DISEASES*

LUDWIK ANIGSTEIN

In this age of mounting technical knowledge when the scientist is driven to specialty and the teaching curriculum of the student is overcrowded with names, a revision of biologic nomenclature is more needed than ever before. Whereas the goal of taxonomy is the orderly arrangement of organisms, its modern trend places emphasis on simplicity and direct usefulness of classification. Nomenclature, as an indispensable tool of taxonomy, should be accessible and available to all scientists of the world with the understanding that the use of technical names should conform to certain rules formulated by international agreement.

Codes of nomenclature were established by international bodies of biologists as to how these names shall be created and used. It was not until 1930 when international opinion was expressed in the matter of bacterial nomenclature at the First International Congress on Microbiology held in Paris. A permanent international nomenclature committee was then established to pass upon suggestions and to make recommendations.

The following are the guiding principles upon which the international rules of botanical nomenclature applicable to bacteria and related microorganisms are based.

The essential points are: (1) to aim at stabilization of names; (2) to avoid the use of names which may cause error or ambiguity or throw science into confusion (Bergey, 1939). Next in importance is the avoidance of all useless creation of names. While we are fully aware that no code is infallible, it is evident that the confusion in nomenclature can be avoided if these fundamental principles are obeyed.

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*From the Department of Preventive Medicine, The University of Texas Medical Branch, Galveston. Presented at the First Inter-American Congress on Typhus, Mexico City, October 7-13, 1945.

The controversial points which exist in rickettsial nomenclature and taxonomy of rickettsiae are due not only to the incomplete knowledge of their biological properties, but also because of negligence of nomenclatorial procedure. This applies to the designation of etiological agents as well as of rickettsial diseases.

As to the position of the pathogenic rickettsiae in the system of microbiology, the bacterial family *Rickettsiaceae* has been suggested by Pinkerton (1936). As long as the morphological criteria dominate in the classification of organisms, there is no reason to separate the rickettsiae from bacteria, although in their metabolic functions the pathogenic rickettsiae behave like viruses. Pinkerton's opinion is shared by Steinhaus in his recent extensive study on "Microbiology of Insects" (in press) where he considers rickettsiae as a peculiar or special kind of bacteria which could satisfactorily, for the time being, be placed in the class *Schizomycetes*, in the order *Rickettsiales*, and in the family *Rickettsiaceae* (personal communication).

While the classification of the rickettsiae as a group seems to be legitimate in complying with the taxonomic practices, the use of the specific names of the respective pathogenic agents is still in a somewhat chaotic state.

There is a complete agreement as to the nomenclatorial stability of the genotype species *Rickettsia prowazeki* Rocha Lima 1916, but the specific status of the murine typhus rickettsia is still subject to controversy. The question still remains whether the causative agent of murine typhus should be *R. mooseri* Monteiro 1931, or *R. prowazeki* var. *mooseri* Pinkerton 1936. The supporters of the varietal status of the murine rickettsia being influenced by the "unistic theory" of Nicolle consider the louse-borne and flea-borne typhus fevers as varieties of the same disease. Irrespective of the philosophical aspect of the possible origin of louse-borne typhus from the more ancient and apparently more complete murine type the question arises whether we are justified to change the specific designation of *R. mooseri* Monteiro, in demoting it to a mere varietal status.

The large volume of experimental researches on *R. prowazeki* and *R. mooseri* brought ample evidence of deep-seated biologic and pathogenic differences between these two organisms. These known distinguishing features have been previously listed and analyzed by Pinkerton (1942) who considers them as "constant and important."

Since that time significant results in this direction have been achieved by the use of the complement fixation method (Plotz, 1943; Topping, Bengston and Henderson, 1945). It was found by Plotz that in 43 human cases of murine typhus 36 gave a positive fixation with murine rickettsia antigen and a negative fixation with louse-borne antigen. In 29 cases of louse-borne typhus 26 gave a positive fixation with louse-borne rickettsia antigen, and a negative test with murine. Plotz concludes, therefore, that the murine rickettsia antigen pattern is different from that of the louse-borne rickettsia.

Furthermore, the recent report by Topping, Bengston and Henderson (1945) on the toxic substance produced by typhus rickettsiae demonstrates its strict antigenic specificity for the respective rickettsia. On the basis of immunity and neutralization tests, murine typhus was clearly differentiated antigenically from louse-borne typhus.

In addition, the failure of vaccines to protect guinea pigs against the heterologous strain was also demonstrated.

In analyzing the above facts it seems that the differences between the louse-borne and flea-borne rickettsiae are of sufficient magnitude to consider them as biologic species of good standing. Should this be accepted the nomenclatorial procedure would require the use of the original name *R. mooseri* Monteiro, which was first assigned to the causative agent of Mexican typhus. However, as pointed out by Philip (1943) this and other synonyms are antedated by *Dermacentroxenus typhi* Wolbach and Todd 1920, in their studies of Mexican typhus. Steinhaus in his "Microbiology of Insects" agrees with Philip that since no intranuclear parasites were reported by Wolbach and Todd the name *typhi* may be transferred to the genus *Rickettsia* as *R. typhi* Wolbach and Todd, or *R. prowazeki* var. *typhi*.

The need for stabilization of names is also increasingly felt in the confusing terminology of rickettsial diseases. As we know, several synonyms of typhus fever are in use designating louse-borne typhus as classic, historic, exanthematic typhus and epidemic. The flea-borne typhus is also listed under the names of murine typhus, tabardillo, shop typhus and endemic typhus (Felix, 1942).

It is questionable whether the commonly used terms of epidemic and endemic typhus fevers serve the purpose of uniformity in reporting causes of death and whether they actually illustrate the intrinsic characteristics of these diseases. It is true that the tendency of louse-borne typhus to assume epidemic proportions is impressive and alarming, but it does not constitute its constant character. On the other hand, murine typhus may occur in mass outbreaks associated with certain environmental factors (Anigstein, 1944). For these reasons it would appear more appropriate if the designation of louse-borne and flea-borne typhus fevers would be uniformly adopted. This nomenclature would be also helpful to the student not only to memorize, but also to correlate the diseases with the important and specific epidemiologic factors.

The nomenclature of the tick-borne rickettsioses suffers again from abundance of terms, most of which are synonyms of spotted fever. The list is rich in geographic names, such as Tobia fever, Kenya typhus, Sao-Paulo typhus, South African tick-bite fever, Mediterranean or Marseille fever. The main characteristic of this group represented by the Rocky Mountain spotted fever is that irrespective of locality, even if separated by thousands of miles, their natural vector is a tick, and the causative agent the intranuclear rickettsial organism, *Dermacentroxenus rickettsi* Wolbach 1919, which is the type species.

Considerable work on the identification of various members of the spotted fever group by reciprocal cross-immunity tests has established the identity of spotted fever strains of the Western hemisphere irrespective of the various tick-vectors. Consequently, *D. rickettsi* is considered as the common causative agent of spotted fever in North, Central and South

America, unless further studies should reveal differences in the antigenic pattern of the particular strains of the agent.

As to the taxonomy of the tick-borne rickettsioses of other parts of the world there are indications that fievre boutonneuse differs in clinical and immunological respects from the western spotted fever. Although a reciprocal cross-immunity between Rocky Mountain spotted fever and fievre boutonneuse has been established by Parker (Pinkerton, 1942) a vaccine protecting guinea pigs against American spotted fever is ineffective against fievre boutonneuse. From the clinical aspect the presence of a localized primary lesion in fievre boutonneuse is emphasized as a point of difference. However, it is questionable whether major importance should be ascribed to this symptom which was misleading in our previous attempts to differentiate on similar lines tsutsugamushi from "scrub typhus."

The causative agent of fievre boutonneuse, originally named *Rickettsia conori* Brumpt 1932, has been changed later to *Dermacentroxenus rickettsi* var. *conori*, Alexander and Mason 1939. According to Pinkerton (1942) and Philip (1943) the varietal or subspecific name of *conori* should be retained. Recent study of Plotz, Reagan and Wertman (1944) has shown that it is possible by means of complement fixation test to differentiate fievre boutonneuse from Rocky Mountain spotted fever. There is, however, some cross fixation which indicates that these diseases are antigenically related.

Finally, confusion is not lacking in the terminology of the mite-borne rickettsiosis named Tsutsugamushi by Hayashi apparently as early as 1906. This disease entity is also described under the following names: Japanese river fever, Kedani fever, tropical typhus, rural or scrub typhus, pseudo typhus, mite typhus, glandular fever, coastal fever. It is obvious that the abundance of synonyms is not helpful in teaching, and is bound to bring confusion in statistical recording of cases. In the recent extensive literature on tsutsugamushi based on the experience from the Pacific War, we find the disease described under the name "scrub typhus."

Any term restricted to this disease entity would facilitate mutual understanding, but its designation by the ecologic factor such as "scrub," although characteristic but not specific, is not very useful. If a selection be made among other synonyms the name *tsutsugamushi* disease claims priority and should be retained.

The taxonomy of the causative agent also awaits more unanimity of opinion. It appears that the organism was probably first observed by Hayashi as early as 1907. In his later publication Hayashi (1920) described the agent as *Theileria tsutsugamushi* noting its pleomorphic nature. Finally, Ogata (1930) describing *Rickettsia tsutsugamushi* as the etiologic agent of tsutsugamushi disease identified it with *Theileria tsutsugamushi* and concluded that the correct name should be *Rickettsia tsutsugamushi* Hayashi 1920 (Farner and Katsampes, 1945). However, the situation became complicated when Nagayo and his co-workers (1930) proposed *Rickettsia orientalis* for the organism which they demonstrated in the Descemet's membrane of rabbit's eye inoculated with tsutsugamushi virus. It is obvious that the rules of nomenclature were disregarded by Nagayo and that the introduction of a new name was out of order.

It may be said in passing that the author of this review while working on "rural typhus" in Malaya (1929–1930) clearly demonstrated the rickettsial nature of the agent in the tunica vaginalis of infected guinea pigs. However, he resisted the temptation to create a new name, anticipating that the disease might prove identical with tsutsugamushi (Anigstein, 1933).

The author agrees with Pinkerton (1942) that both names *R. tsutsugamushi* Hayashi 1920 and *tsutsugamushi* disease should be retained. This opinion is shared by Steinhaus who considers that "the correct name of what is commonly called 'scrub typhus' to be *tsutsugamushi* disease, and that correct species of the rickettsia is *R. tsutsugamushi*" (personal communication). An identical viewpoint was recently expressed editorially (U. S. Naval Med. Bull., Jan. 1945, p. 178–180).

Summary and Recommendations

An attempt has been made to analyze the taxonomic and nomenclatorial problems of the more important rickettsial diseases and their agents. It was found that in spite of the impressive progress in rickettsiology a further elucidation of the specific characters of the agents as biologic entities is necessary for adequate taxonomic differentiation. It is felt, however, that the present confusion in nomenclature is not so much caused by our incomplete knowledge as by the disregard or negligence of taxonomic and nomenclatorial rules.

It is suggested that a technical Inter-American committee should be assigned the task of making adequate recommendations for a uniform and coördinated nomenclature. The proposed revision should be guided by its practical usefulness for didactic purposes as well as for the uniformity in recording riskettsial diseases.

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FUNCTIONAL MITRAL DIASTOLIC MURMURS*

GEORGE M. DECHERD, JR., AND OWEN W. BEARD

Exceptions are often erroneously said to prove the rule, but it is rare that an opportunity really arises to show an exception to the well-established rule that diastolic murmurs are diagnostic of cardiovascular disease. Certainly the presence of a diastolic murmur at the apex of the heart has been taken to indicate, with a high degree of accuracy, the presence of rheumatic mitral stenosis. The well-known Austin Flint phenomenon is not uncommonly encountered in patients with aortic insufficiency. Other causes of apical diastolic murmurs without rheumatic mitral stenosis are less commonly recognized. Recent experience has allowed us to collect several instances of stethographically proven mitral diastolic murmurs in patients subsequently proven not to have stenosis of the mitral ring. These cases illustrate several of the types of cardiac affection likely to lead to this diagnostic error.

Case 1. J. S., a negro man 52 years of age, John Sealy Hospital Unit History No. 71566, was first seen in 1922 in the Out-Patient Clinic with gonorrheal urethritis. In 1931 the blood Wasserman reaction was positive; he did not return for antiluetic treatment until 1938. At that time he was found to have aortic insufficiency, with a high-pitched aortic diastolic murmur which was transmitted to the apex; there the murmur was changed in quality to a lower pitched rumble with presystolic accentuation. A teleoroentgenogram showed widening of the aortic shadow, and an electrocardiogram showed left axis deviation with a negative T wave in Lead I. There was no clinical evidence of cardiac failure.

The stethogram, recorded on March 25, 1944, showed transmission to the apex of the high-pitched aortic diastolic murmur which occupied nearly the whole of diastole. Just before the first sound the pitch became lower, and there was an increase in the amplitude of the sounds (Fig. 1A).

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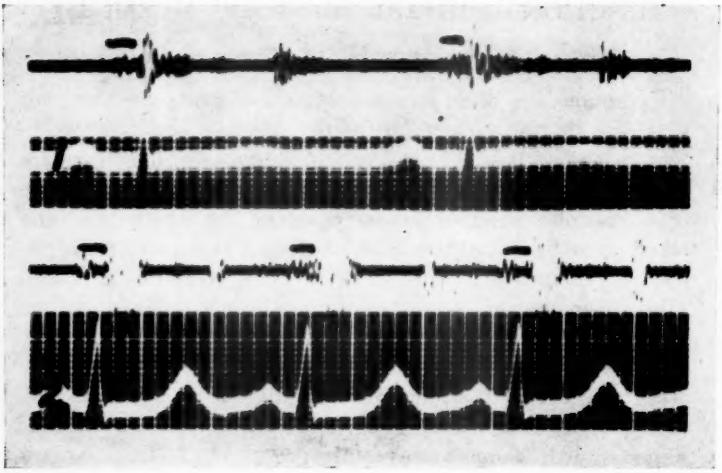

Figure 1. Cases 1 and 2; the solid line indicates the Austin Flint murmur. In each figure the stethogram is recorded above Lead II of the electrocardiogram.

Case 2. S. L., a Mexican man 43 years of age, No. 2552 A. entered the hospital on August 30, 1945, because of severe retrosternal pain which radiated down both arms. This had been present for 3 months, and was precipitated by exertion. The blood Kolmer reaction was positive. Examination of the heart showed an aortic diastolic murmur which was transmitted along the left sternal border to the apex. At the mitral area the murmur was changed in pitch, and showed a presystolic accentuation. The electrocardiogram showed depression of the ST segments in Leads I and 4F, with a deep negative T wave in Lead 4F. There was a large Q wave in Lead CF_2.

The stethographic records (Fig. 1B) revealed that the diastolic murmur occupied all of diastole. At the apex it became lower in pitch and louder in the presystolic interval.

Comment. These curves illustrate the change in the quality of the murmur of aortic insufficiency as it is transmitted to the apex of the heart—a change with crescendo presystolic

accentuation which closely imitates the signs of organic mitral stenosis. This was first described by Austin Flint in 1862 on the basis of a study of syphilitic aortic insufficiency at Charity Hospital in New Orleans; it was the first recognized functional mitral diastolic murmur. The exact mechanism of its production is not positively established, but it is generally accepted that the aortic leaflet of the mitral valve participates in its pathogenesis. The valve leaflet may be caught in vibrations set up by the turbulent mingling of the regurgitant stream of blood entering the ventricle from the auricle; or the regurgitant stream may push the leaflet into a partially closed position, thus in effect producing a functional obstruction. The experimental evidence of Herrmann (1926) suggested that lesions of the posterior aortic leaflet gave rise to a regurgitant stream whose direction caused the Austin Flint murmur. However, Gouley's study (1941) of human material indicates that the Flint phenomenon is associated with defects in the right anterior aortic cusp. This discrepancy may well be due to the difference in posture, and of the position of the heart, in man and animal.

Case 3. L. S., a negro girl 12 years of age, No. 5584 B, was admitted to the hospital June 6, 1945. Two months previously she had experienced right lower abdominal pain associated with nausea and vomiting, for which an appendectomy was done. Recovery was uneventful. Two weeks later she developed pneumonia which was treated with penicillin. Fluid was withdrawn from her right pleural space on two occasions. In the preceding five years she had had repeated episodes of migratory polyarthritis.

When examined the child was found acutely ill, with respiratory distress and with her voice diminished to a hoarse whisper. There were signs of pleural thickening over the right lung base. The heart was enlarged, with the apex in the anterior axillary line. A loud systolic murmur could be heard at all valve areas, and at the apex there was a gallop sound with a diastolic murmur (Fig. 2A). The electrocardiogram showed prolongation of the PR interval to 0.20 sec. with the rate at 120 per minute. There were 2.3 million

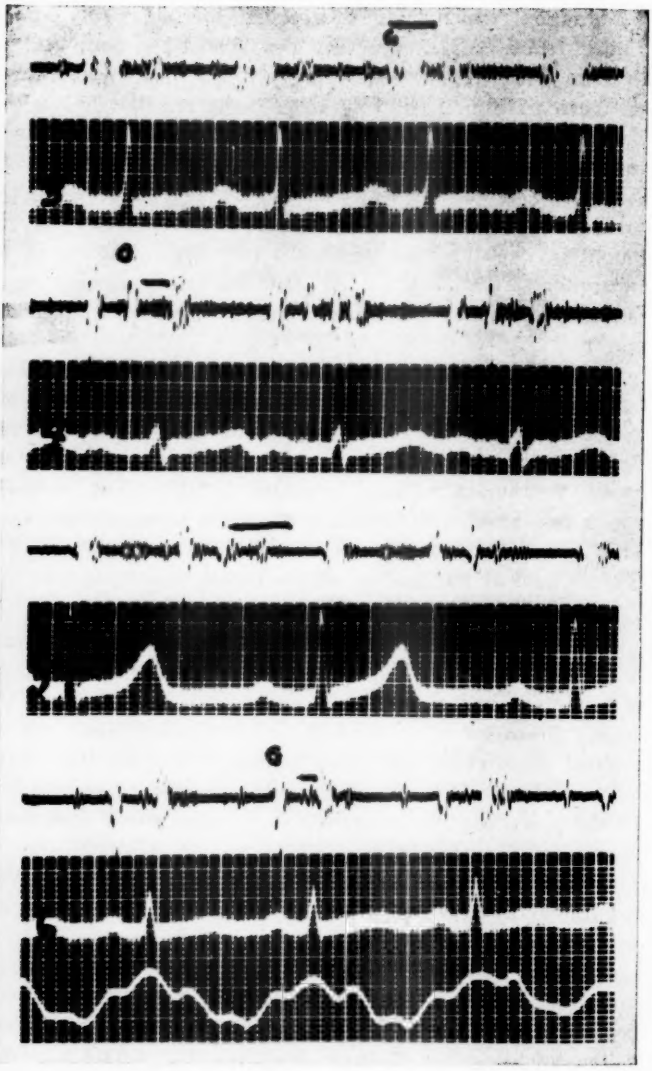

Figure 2. Cases 4-6. The diastolic murmurs are marked. G indicates the gallop sounds. The simultaneous jugular pulse record is shown with the stethogram and electrocardiogram of Case 6.

red blood cells per cu. mm., with 7.7 gm. of hemoglobin per 100 cc. White blood cells were 8.350 per cu. mm., with 78% polymorphonuclear cells. The red cells showed no sickling; the sedimentation rate was 36 mm. per hour. The urine examination showed no abnormalities except a trace of protein.

Therapy consisted of sodium salicylate, oxygen, digitalis, and sedation. Fever persisted, the dyspnea became progressively worse, and choreiform movements appeared. Death occurred July 11, 1945.

Necropsy was performed on the day of death. The heart weighed 600 gm. The parietal pericardium was adherent to the heart over limited areas both posteriorly and laterally. The remainder of the pericardium showed fibrinous pericarditis. The ventricles were hypertrophied, and greatly dilated. The mitral ring had a circumference of 10.5 cm. The mitral leaflets showed small acute rheumatic vegetations along their lines of contact. There was edema of the lungs, chronic passive congestion of the liver, and a chronic penetrating peptic ulcer in the posterior duodenal wall.

Comment. This is a classical example of a loud apical diastolic murmur in a child with acute rheumatic myocarditis, without mitral stenosis. An adherent pericardium was blamed by Fisher (1894) for the diastolic murmur heard in five children whose mitral valves did not show stenosis. Phear (1895) collected 19 similar cases, but he pointed out that the adherent pericardium was always associated with dilatation of the ventricle. In an additional ten of his cases with such a murmur, dilatation of the left ventricle appeared to be the chief causative factor, since neither aortic insufficiency nor adherent pericardium were present. The role of cardiac dilatation in producing a functional apical diastolic murmur was again pointed out by Wood and White (1923), of whose four cases only one had pericardial adhesions. According to their concept, dilatation of the left ventricle in the presence of vigorous action of the heart, produced in effect a relative stenosis of the mitral orifice. The transient nature of such

murmurs heard during the course of acute rheumatic myocarditis was emphasized by Bland, White, and Jones (1935) and again by Bland, Jones, and White (1936). These authors pointed out that since several years are required for valvular scarring to produce actual stenosis, the apical diastolic murmurs heard during the course of acute rheumatic carditis must be due to relative stenosis of the mitral aperture, when considered in relation to the dilated ventricle. This is supported by the large group of patients in whom the murmur disappeared, and by other instances in whom necropsy showed left ventricular dilatation in the absence of mitral obstruction. The same conclusions were reached by Weinstein and Lev (1942), who pointed out that often the left auricle was likewise greatly dilated. The most striking demonstration of such dilatation in the auricle was its enlargement in one case until it formed part of the right heart border, and in another, enough to press on the recurrent laryngeal nerve to cause hoarseness, such as was seen in the case described above. Dilatation of both the auricle and ventricle readily permits the concept of relative stenosis of the fixed fibrous mitral ring.

Case 4. H. C., a Mexican boy 14 years of age, No. 3202 B, was admitted April 12, 1945 because of abdominal pain, ankle edema and epistaxis. He was emaciated; there was a generalized lymphadenopathy; the axillary glands were 3 cm. in diameter. On admission the heart was not enlarged, though there was a loud harsh systolic murmur heard at the apex and at the pulmonic area, with a loud gallop sound. The spleen was enlarged, and there was ascites, and edema below the knees. The red blood cells were 1.2 million per cu. mm. with 4.1 gm. of hemoglobin per 100 cc. White blood cells were only 800 per cu. mm.; 66% were polymorphonuclears. A-V conduction was prolonged to 0.20 sec. with a heart rate of 110 per minute. Histologically, a lymph node suggested Hodgkins' disease, while the bone marrow biopsy was interpreted as indicating an acute leukemia. Administration of penicillin failed to lower the temperature, and numerous blood

transfusions failed to alter the down-hill progress. Death occurred on the 17th hospital day.

The stethogram (Fig. 2B) taken over the mitral area shows a systolic murmur of moderate intensity. The second sound is accentuated, and is followed by a loud gallop sound. After the gallop a low pitched diastolic murmur is recorded.

At necropsy the tissue sections showed miliary tuberculosis. The heart weighed 240 gm. and was greatly dilated. The mitral ring was 10 cm. in circumference; all valve leaflets were normal. Microscopically, the myocardium showed albuminous parenchymatous degeneration. The liver (1500 gm.) and the spleen (1100 gm.) were enlarged.

Comment. The literature on cardiac manifestations in anemia has recently been summarized by Carter and Traut (1943), who reviewed 300 cases of Addisonian anemia from the standpoint of their cardiovascular manifestations. Twelve of these patients had apical diastolic murmurs; however, patients with organic heart diseases were not excluded so it cannot be ascertained whether or not these murmurs were functional. Dilatation of the heart in severe anemia was noted by Ball (1930) and by Tung et al. (1937), and Goldstein and Boas (1937) reported the occurrence of diastolic murmurs. Gunewardene (1933) noted the presence of apical murmurs during diastole in patients with severe anemia due to hookworm disease; these murmurs disappeared after treatment. This is another instance of relative mitral stenosis.

Case 5. D. J., a negro boy 8 years of age, No. 79882, had been frequently admitted to the hospital since the age of 5 years. His mother described numerous episodes of sore throat, fever, dyspnea, and scleral jaundice. There was slight clubbing of fingers and toes. He was found to have persistently icteric sclerae, hepatomegaly and enlargement of the heart. The cardiac apex was in the anterior axillary line. The pulmonary second sound was accentuated, and there was a systolic murmur to be heard all over the precordium. At the apex there was a gallop sound, and a low-pitched diastolic murmur. An anemia was present, associated with sickling of the red blood cells.

On November 29, 1944 the boy was readmitted in a hemolytic crisis. He was febrile, and complained of pain in the abdomen and legs. His left knee was hot, swollen, and tender. The sclerae were jaundiced, with an icteric index of 51; the liver was enlarged, but the spleen could not be felt. The venous pressure was elevated, and the lungs showed signs of passive congestion. The red blood cells were 1.6 million per cu. mm. The electrocardiograph showed prolongation of the PR interval for the child's age and heart rate.

The stethogram showed a gallop rhythm and a diastolic murmur (Fig. 2C).

Comment. It cannot be said with certainty that this child does not have coincident rheumatic valvulitis. His younger brother also has sickle cell anemia, with an apical diastolic murmur, and similar murmurs have been recorded in other patients. It should be pointed out that sickle cell anemia not uncommonly gives rise to signs suggestive of rheumatic heart disease (Hein, McCalla, and Thorne, 1927; Klinefelter, 1942), but that the pathologic confirmation of the presence of rheumatic carditis is very rare. The cardiac features of sickle cell anemia have been studied by Klinefelter (1942) and Winsor and Burch (1945). The first patient noted to have a functional diastolic murmur was that described by Hamman (1932). Since that time the similarity of the cardiac findings in sickle cell anemia to those in rheumatic heart disease has been frequently noted; this is particularly confusing, since other clinical and electrocardiographic features may also be similar in the two diseases. The actual concurrence of the two diseases is rare, having been demonstrated only by Steinberg (1930), Walker and Murphy (1941), Mallory (1941), and Greenwald, Spielholz, and Litwins (1943).

Functional apical diastolic murmurs are more frequent in our experience in sickle cell anemia than in other varieties of anemia. Dilatation of the heart seems to be present more often; and the fever present during the hemolytic crisis probably speeds up further the already accentuated rate of blood flow. It seems likely that relative mitral stenosis due

to left ventricular dilation, when associated with rapid rate of blood flow, leads to the formation of eddy currents and murmurs as the blood flows through the mitral orifice.

Case 6. J. L., a negro woman 21 years of age, No. 35733, was admitted to John Sealy Hospital February 8, 1945 with a story of painful joints for about 5 months. On previous admissions she had a tonsillectomy in 1931; a fracture of the right humerus in 1931; had delivered a premature male infant in 1940 followed by an acute hepatitis ascribed to preceding injections of neoarsphenamine; drainage of a pelvic abcess by colpotomy in 1941. The gonococcus was cultured from the cervical discharge.

In September 1944 she had painful swollen ankles; a week later her knees were similarly affected. These joint symptoms disappeared in about two months. At the time of her last admission the joint pains had returned, though there was no objective swelling. The rectal temperature was 105° F., but reached normal on the 5th hospital day after the administration of sodium salicylate 1.5 gm. six times daily. The blood salicylate level reached 0.57 mgm. per cc.

The blood pressure was 130/80; the rhythm regular; the heart rate 120 beats per minute. A systolic murmur was heard over the whole precordium but loudest at the apex of the heart. At the apex there was also a faint presystolic murmur. A gallop rhythm was present. There was no evidence of congestive heart failure, although the heart was enlarged towards the left.

The red blood cells were 2.4 million per cu. mm.; hemoglobin was 6.6 gm. per 100 cc. The white cell count was 7,050 per cu. mm., with 53% polymorphonuclear cells, 44% lymphocytes and 3% monocytes. The urinary specific gravity was 1.029, protein was 3+, sugar was absent. Blood culture was negative. On February 13, shortly after the temperature reached normal, the patient had two convulsive seizures, which were repeated several times daily thereafter. Sodium salicylate was stopped, and when the temperature rose to 106° F. rectally on February 15, phenacetin was given. She

became stuporous and incontinent, with continuous choreiform movements of the extremities. The spinal fluid was examined on February 15; the pressure was normal, the appearance xanthochromic; there were two cells per cu. mm., one lymphocyte and one polymorphonuclear cell; the protein content was 150 mgm. per 100 cc.; the colloidal gold curve was reported as 4455544; the Wassermann reaction was anticomplementary. The white blood cells rose on February 16 to 14,300 per cu. mm. with 79% polymoruclears. Death occurred on February 19.

The clinical impression was rheumatic fever with rheumatic myocarditis and mitral valvulitis, and toxic encephalitis due to sodium salicylate.

The electrocardiograms showed no definite abnormalities on February 8 and February 9; on February 13, T_1 had become lower, almost isoelectric, and the T waves in leads CF_2 and 4F had become negative.

A stethogram was recorded on February 9 (Fig. 2D). Systolic murmurs were present in each valve area, and gallop sounds were noted in the tricuspid and mitral areas, and in the mitral area there were vibrations suggesting a presystolic murmur.

At necropsy the heart weight was 270 gm. The ventricles were moderately dilated; otherwise there were no abnormalities. There was some edema between the muscle fibers histologically. The liver showed focal necrosis, and the lungs contained confluent patches of bronchopneumonia. The brain was edematous, with pericapillary hemorrhages.

Comment. The cause of the marked ventricular dilatation remains obscure; certainly the histologic findings offer little help. It is equally clear that there was no narrowing of the mitral ring. In fact, it was debatable clinically. There was an unusually loud gallop sound heard during the phase of rapid ventricular filling. Whether the additional sound heard just before the first sound was a gallop synchronous with auricular systole, or was a short presystolic murmur could not be decided with the stethoscope. The stethogram does not permit a final decision, i.e. it is impossible to say whether the second

diastolic sound is a gallop or a short murmur. Its timing at the peak of the a-wave of the jugular pulse is proper for an auricular gallop. On the other hand a presystolic murmur would appear in the same place. The clinical circumstances, with dilatation of the ventricular myocardium, would allow either possibility. We interpreted this as a functional presystolic murmur, but have included it particularly for the purpose of illustrating this possible source of error, both clinically and stethographically.

Case 7. E. H., a negro man 28 years of age, No. 4929 B entered the hospital on June 2, 1945 complaining of dyspnea and chest pain. His symptoms had begun with a cold three months before; following this, pain in the chest had appeared, with dyspnea on exertion and swelling of his ankle. During this interval he had lost 15 pounds of weight. Twelve years previously his left leg had been amputated below the knee because of a "bone cancer" which followed the kick of a horse.

His neck veins were distended. The apex beat could be felt in the anterior axillary line; at this point there was a blowing systolic murmur, with a lower rumbling diastolic murmur associated with a thrill (Fig. 3). There were signs of atelectasis in the right lung base, and a hard fixed mass was attached to the spine of the right scapula. The liver extended down to the level of the umbilicus; the spleen and kidneys were not palpable. There was marked clubbing of

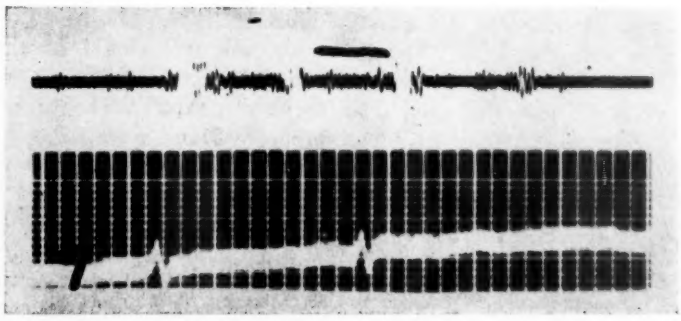

Figure 3. The diastolic murmur of Case 7.

his fingers and of the toes of the right foot. There was a moderate grade of edema of his right leg.

An X-ray of the chest revealed a large tumor mass above the right diaphragm and extending to the mediastinum. The electrocardiogram showed a right axis deviation, auricular fibrillation, and isoelectric T waves in Leads I and II. The circulation time was measured at 60-70 sec. in three tests. The venous pressure was 14 cm. of saline.

A needle biopsy of the lung tumor established it as an osteochondroma, and sections taken from the scapular mass showed an osteochondrosarcoma.

The films of the chest indicated that the heart was pushed far to the left, thus accounting for the position of the apex. In spite of the absence of a history of rheumatic fever, it was thought that the apical diastolic thrill and murmur, associated with electrocardiographic evidence of a right axis deviation and auricular fibrillation, adequately supported the diagnosis of mitral stenosis. Digitalis was pushed to the point of intoxication, manifested by anorexia and nausea, and by the development of paroxysmal auricular tachycardia with 2:1 A-V block. However, the ventricular rate was never successfully lowered to 90 beats per minute.

Necropsy showed the enormous chondrosarcoma occupying the lower portion of the right chest and extending through the mediastinum into the left lung, and into the pericardium. The intra-pericardial portion surrounded the pulmonary veins and was fixed to the adjacent auricle. It did not penetrate the auricular wall. The heart was not separated from the mass, and hence its weight was not determined. It was not enlarged and the valve leaflets were normal. The mitral orifice was 10 cm. in circumference. There were 1200 cc. of bloody pericardial effusion, with a thin layer of fibrin on the epicardium.

Comment. Ludwig (1933) and White (1944) mention as a rare cause of a functional mitral stenosis the occurrence of a tumor or thrombus in the left auricle large enough to obstruct the mitral ring. The enormous tumor found in the

present patient did not penetrate the auricle. A nodular mass 4.5 by 6 by 10 cm. was inside the pericardial sac, and was adherent to the entire posterior auricular wall, surrounding the pulmonary veins. The tumor greatly distorted the auricle itself and may well have given rise to eddy currents in the blood flowing through the auricle. Its presence however, also distorted the mitral ring, giving to its posterior half a rigidity which interfered with normal opening.

Case 8. R. Z., a white boy 5 years of age, was seen on September 26, 1944 for an examination preliminary to tonsillectomy. He had had numerous attacks of sore throats since he was one and a half years of age. At that time his physician had noted the presence of heart disease. Aside from a supernumerary right thumb and greatly enlarged tonsils, the chief points of interest pertained to his heart.

The sternum and ribs bulged forward at the level of the 4th costo-sternal junction. The cardiac apex was in left 5th interspace at the anterior axillary line. There was a systolic thrill felt over a large area, maximal just above the 4th rib, 2.5 cm. to the left of the mid-sternal line. A loud harsh systolic murmur could be heard over the whole precordium and below the left scapula, but was loudest at the point of maximal intensity of the thrill; there was no diastolic murmur at this point. In addition, at the apex there could be heard a low rumbling middiastolic murmur (Fig. 4A). Fluoroscopy showed that the barium filled esophagus was not distorted by any enlargement of the left auricle.

The electrocardiogram showed a moderate degree of right axis deviation. The PR interval was barely within normal limits for this child's age and heart rate.

Case 9. J. S., a white boy 6 years of age, No. 7939 B, was seen on September 12, 1945. He had been seen by a physician in the preceding June because of abdominal pain; at that time it was noted that he had heart disease. He had had no symptoms referable to his heart.

He was well developed and appeared healthy. No abnormalities were noted except in his cardiac examination. The heart was slightly enlarged towards the left. There was a

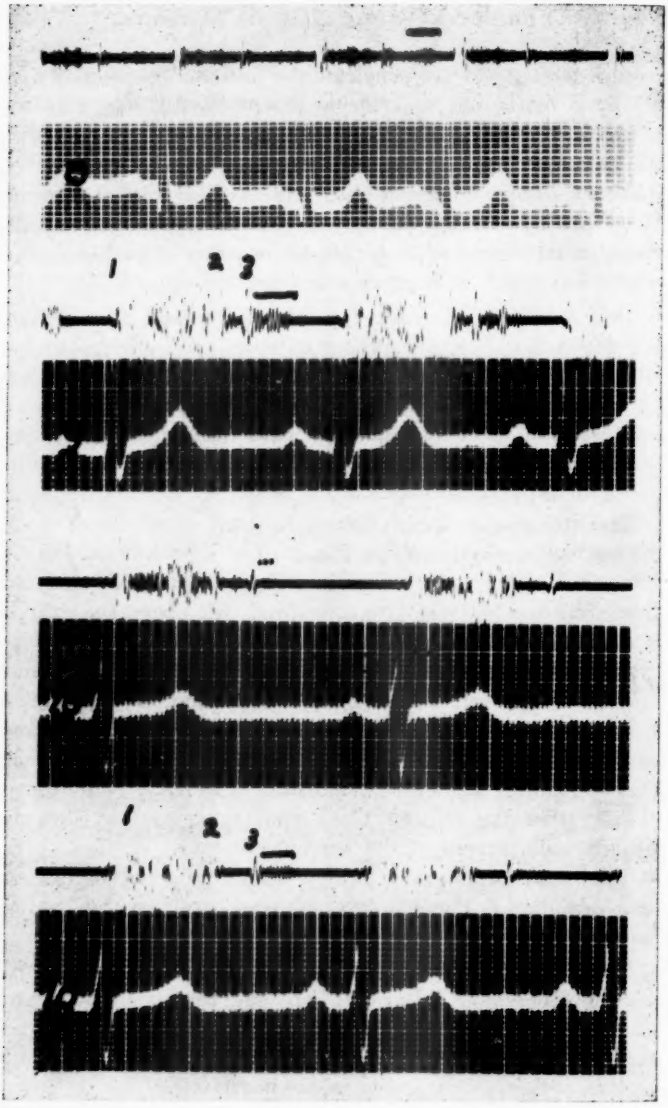

Figure 4. Cases 8-10. The diastolic murmurs are indicated. 1, 2, 3, indicate the heart sounds. The last strip (10B) shows the accentuation of the diastolic murmur after exercise; compare with the preceding strip (10A).

conspicuous systolic thrill, palpable best in the 3rd and 4th left interspaces near the border of the sternum. Synchronous with the thrill, there was a rasping murmur of a similar distribution. In addition, at the apex there was a softer lower-pitched early diastolic murmur (Fig. 4B). This murmur was sharply localized to the apical region, was better heard in the left lateral position, and was exaggerated by exercise. The electrocardiogram was normal. Fluoroscopy confirmed the fact that the transverse measurements of the cardiac shadow were lightly increased. The enlargement was thought to be in the right ventricle; the left auricle was normal in size.

Case 10. A. R., a white boy 14 years of age, No. 47372, entered the hospital on September 1, 1945 because of a laceration of his left foot. He had been seen previously on numerous occasions and the existence of an inter-ventricular septal defect had been recognized at the age of 3 years. In addition he had been found to have a spina bifida occulta, and the intellectual level of a moron. Cardiac symptoms were limited to the presence of dyspnea on strenuous exertion.

The apex of the heart was in the 6th left interspace 5 cm. from the mid-sternal line. There was a systolic thrill, maximal in the 4th left interspace near the sternal border, associated with a loud harsh systolic murmur. The presence of a faint diastolic murmur at the apex was debatable (Fig. 4C), but after exercise it was clearly heard in the left lateral position (Fig. 4D).

Comment. The typical murmur of a defective inter-ventricular septum is systolic in time, harsh and rasping in quality, and is usually maximal in the third or fourth left interspace near the left sternal border. A small percentage of the patients may also have a much fainter diastolic murmur at this point. We have searched the literature on the subject exhaustively and although it seems quite possible that we have overlooked it, we have been unable to find any description of an apical diastolic murmur in Roger's disease. The murmur is heard early in diastole, is low and rumbling, and is sharply localized. It is accentuated by the left lateral

position, and by exercise, just as is the murmur of organic mitral stenosis.

We conceive of this as a functional mitral stenosis. The papers of Burwell, Eppinger, and Gross (1941) and Eppinger and Burwell (1940) have given data which seem pertinent. Their studies of the pulmonary circulation in patients with patent ductus arteriosus, before and after ligation of the duct, have shown that as much as 77% of the blood leaving the left ventricle may be shunted back through the lungs. They note that one of their patients had a mitral diastolic murmur which disappeared after ligation.

It seems reasonable to believe that a defect in the interventricular septum similarly permits a large amount of blood to be shunted from the general circulation back through the lungs. In fact, one set of measurements recorded by Burwell (1941) shows that 35% of the blood leaving the left ventricle was shunted back through an I-V septal defect produced experimentally in a dog. It follows that the rate of flow of such an increased volume of blood must be accelerated when it passed through a fixed aperture such as the fibrous mitral ring. Bramwell (1943) has reported that an increased rate of blood flow induced by exercise will produce a presystolic murmur simulating that of mitral stenosis.

In Cases 8, 9, and 10 necropsy proof of normal mitral valves is lacking. However mitral stenosis seems to us to be satisfactorily excluded on clinical grounds. We postulate that when the pulmonary blood flow is increased greatly, the normal mitral orifice is relatively stenotic, thus producing the low pitched diastolic murmur.

Discussion. We have no stethographic record of a functional mitral murmur of the type described by Wyckoff and Bunim (1935). These authors found that pulmonary hypertension caused great hypertrophy of the right ventricle; the septum bulged into the cavity of the left ventricle so as to cause, in effect, a narrowing of the ventricle itself, thus producing an apical murmur. In discussing this paper, Christian stated that the cardiac hypertrophy associated with hyper-

tension might give rise to murmurs indistinguishable from those of mitral stenosis.

The instances of functional apical diastolic murmur that we have recorded fall into several large categories. First, is the Austin Flint murmur, seen only with aortic insufficiency. Second, is the murmur heard with great dilatation of the left ventricle, due to various types of myocarditis, notably rheumatic, or to anemias, notably sickle cell anemia. It seems probable that the acceleration of blood flow associated with anemia may contribute to the functional murmur as much as does the ventricular dilatation. The fever associated with sickle cell crises is an additional factor that accelerates blood flow. Third, is the rare instance of distortion of the mitral ring by an extrinsic tumor. Fourth, is the great increase in pulmonary blood flow due to a shunt between the left and right sides of the heart; this has been demonstrated for a patent ductus arteriosus, and seems surely present in the cases of septal defect that we have described.

Such murmurs are of diagnostic significance, and the possibility of their functional pathogenesis may obviously influence the management and prognosis of those patients that exhibit them.

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HISTAMINE—ITS PHYSIOLOGICAL, PHARMACOLOGICAL AND CLINICAL SIGNIFICANCE*

W. A. SELLE†

Histamine—chemically known as β-iminazolylethylamine, a decarboxylation product of the amino acid histidine—is a biological agent of considerable physiological and pharmacological interest but of somewhat doubtful therapeutic value. Being widely distributed in plants and animals, it was first detected in ergot by Barger and Dale (1) in 1910 and subsequently in almost every mammalian tissue. The formation of histamine in the animal body is still not well understood, nor is the manner in which it is combined, stored, and liberated. Present in amounts which are toxic when liberated, it apparently exists in a bound and inactive form in most cells of all animals. Its concentration in lung tissue is particularly high, the physiological significance of which is still unknown. The formed elements of the blood also contain appreciable amounts of histamine. While certain bacteria can convert histidine into histamine—a reaction which may be extensive in the gastrointestinal tract—there is no sound basis for the claim that histamine causes the so-called "autointoxication" syndrome.

Pharmacologically, histamine has a wide variety of actions. There is hardly an organ or tissue which will not respond in some way to this powerful agent. The extensiveness of action, together with the universal distribution of the chemical, has led to innumerable theories of its physiological function. The existence of possible relationships between the pharmacological actions and the physiological significance of histamine will be given consideration as occasion arises in the ensuing review.

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†From the Physiology Laboratory, The University of Texas Medical School, Galveston. Received for publication January 10, 1946.

PART I: GENERAL STATEMENT OF THE CHEMISTRY, PHYSIOLOGY, PHARMACOLOGY AND CLINICAL SIGNIFICANCE OF HISTAMINE

The material which forms the basis of Part I of this review is not entirely new. However, an attempt is made to mold it into something approaching a useful pattern. In a resumé of this scope it is not possible to review all papers or to cite references for statements generally accepted or regarded as uncontestable.

A statement of the chief pharmacological actions of histamine on the body involves the cardiovascular, respiratory, gastrointestinal and urinogenital systems. The response produced on these systems is due chiefly to changes in contractility of the smooth muscle constituents of the tissues composing these systems. Certain effects are due to stimulation of various glands of external secretion. Still other effects are the result of changes in the permeability of capillaries.

Cardiovascular System

a) *Blood Vessels*

Histamine is a powerful dilator of capillaries, an action which is direct on the contractile mechanism. The response of the capillary is independent of innervation and is uninfluenced by blocking drugs such as atropine. The histamine response of the vessel is generally increased, however, after denervation. Large doses of histamine dilate the capillaries and increase permeability. This results in a loss of plasma protein and fluid through the capillary wall into the extracellular areas and in stagnation of blood within the vastly enlarged capillary bed. As the capillaries of the skin are no exception to the dilator action of the drug, the skin becomes red and the surface temperature rises.

Intradermal injection results in a local reaction, similar to the triple response of various types of cutaneous stimuli. This consists of 1) a local red area resulting from active dilatation of capillaries by direct contact with the drug, 2) a diffuse flare due to dilation of surrounding arterioles by local axon reflexes,

and 3) ultimately a wheal or area of edema due to transudation of fluid from the capillaries involved previously in the red reaction. The cutaneous reactions following injuries of various sorts, e.g., burning, freezing, electrical stimulation, and the more slowly erythema resulting from ultra-violet irradiation, are believed by Lewis (2) to be produced by histamine or a histamine-like substance (H substance) liberated by the injured cells of the epidermis.

The action of histamine on arterioles is variable for different animal species. Arterioles of rodents are markedly constricted, those of the cat slightly constricted, and those of the dog, monkey, and man dilated. Stead and Warren (3) found that histamine injected intra-arterially into man increases the permeability of the capillaries supplied by the artery. The rapid loss of protein from the plasma can be detected by comparing the blood draining from the part before and after the injection. The hematocrit reading and hemoglobin concentration usually increase markedly while the protein concentration rises only slightly.

The marked dilatation of the microscopic vessels, with or without a concomitant reduction in blood volume by loss of plasma into the tissues, results in a drop in blood pressure. Sollmann (4) states that while the blood pressure of the dog, cat, monkey, and of man falls after histamine injection, that of the rabbit and guinea pig rises. Recovery of blood pressure from histamine depression is usually rapid. Such recovery is due to three factors: 1) rapid destruction of histamine in the body, 2) institution of complex, compensatory cardiovascular reflexes, and 3) the discharge of epinephrine. Epinephrine itself can antagonize the vasodepressor action of histamine and some of its other actions.

Administration of large doses of histamine are followed by a precipitous fall in pressure which may be pronounced and persistent, if not fatal. The production of experimental shock by single or repeated injections of histamine is a common procedure. The primary cause of this form of shock is believed by most workers to be due to the loss of a critical amount of plasma from the circulation so that a discrepancy exists between the volume capacity of the circulatory system and the

volume of circulating blood. This discrepancy, if persistent, leads to an abnormal physiology which results in an irreversible failure of peripheral circulation. Such a discrepancy appears to be the basis of several varieties of shock. The relation between histamine shock and traumatic and anaphylactic shock has been the subject of much discussion during the past twenty or thirty years. The fact that the body seems to contain large amounts of inactive or bound histamine has been interpreted by some as suggesting that histamine is the causative agent in traumatic and allergic shock. Aspects of this possibility will be considered in more detail in subsequent pages. At this juncture it may be pointed out that those who maintain that histamine is the causative agent in traumatic shock believe it to be released as a result of extensive tissue damage, and those who implicate histamine in anaphylaxis postulate that the intracellular antigen-antibody reaction results in liberation of histamine and other chemicals.

Besides the general effects on blood vessels, histamine has specific actions on the blood flow of different organs. The action in question, however, often varies with the species. In some animals histamine causes constriction, in others dilatation. In the dog it constricts the hepatic vein.

The action of histamine on the blood vessels of the face and brain is particularly noteworthy. Intravenous injection of 0.001 mg. of histamine per Kg. of body weight causes prompt dilatation of the minute vessels of the face. The time required for this may be used as an index of the blood flow velocity (5). The administered drug also promptly dilates the vessels of the meningies and brain. Accompanying this, there is an increase in cerebrospinal fluid pressure. Frequently a characteristic headache and visual disturbances follow. According to Pickering (6) the pain arises from the dura, the visual disturbances to vasodilation of the retinal vessels and to the resulting increase in intraocular pressure.

Excised arteries are constricted by histamine in most species and in most situations, but not liver veins (4). Pulmonary vessels are constricted in lung sections (7) and apparently even in intact animals, for the pressure in the pulmonary

artery rises and the volume of the lung diminishes, even when the pressure in the systemic arteries is unchanged.

b) *Lymphatics*

At present much interest is attached to the role of the lymphatics in the return of fluid to the blood in conditions of shock and hemorrhage. Histamine administered to dogs by McCarrell and Drinker (8) in doses sufficient to lower the blood pressure to 20 to 60 mm. of mercury increases cervical lymph flow 1.1 to 4.9 times the control values. The total lymph protein increases although the concentration becomes less. Of further interest is the finding that the period of increased protein escape from the blood is temporary and as the histamine shock continues the lymph flow and its protein content return to normal.

Abramson and Engel (9) have stressed the activity of the minute cutaneous lymphatics of man in the mechanism of the spread of histamine wheals, which form not so much by diffusion of histamine through the tissues as by the convection of it by the minute lymphatics. At some distance from the original injection site, histamine escapes from the lymphatics into the tissues to act upon the blood vessels. Some of it may be taken up again into the lymph and carried a little farther through these channels, escape again and to act in the tissues at a still more distant site. Furthermore, Abramson and Gettner (10) have introduced histamine and epinephrine into human skin by electrophoresis with current densities so low that no appreciable tissue injury occurs. In the skin of the forearm epinephrine causes blanching and vasoconstriction, and presumably a decrease in dermal tissue fluid pressure. Nevertheless, the substance is taken up by the intact lymphatics and drained up the arm in the same way that dyes are after they have been injected intradermally (11), (12), (13).

c. *Heart*

The heart is affected little or not at all by moderate amounts of histamine. High concentrations weaken the muscle and produce conduction disturbances. In human subjects, continuously infused histamine at the rate of 0.02–0.04 mg. per

minute usually produces an increase in heart rate and cardiac output which are due to compensatory reflex responses and not to direct cardiac stimulation. Weiss, Ellis, and Robb (14, 5) report that in some subjects the heart rate is increased without change in blood pressure, but with dilatation of the brain and skin vessels. While histamine affects the coronary arteries of various animals differently, constricting some and dilating others, Essex and co-workers (15) have reported that the drug invariably increases the rate of coronary blood flow. Large doses injected intravenously into dogs, cats, rabbits, and guinea pigs dilate the right heart, probably through increased resistance in the lung vessels. Repeated hypodermic injections lead to hypertrophy of the right heart. According to Kirch (16), morphologic changes in the heart tissue are produced both by acute and repeated injections. The perfused mammalian heart shows an initial slight slowing, followed by considerable quickening with increased excursions (4).

Electrocardiographic Changes After Histamine

Massione and Picchio (392), Weiss, Robb and associates (5, 28), and Albers and Petzol (393) report the effects of subcutaneous and intravenous injection of histamine in human subjects having normal and abnormal cardiovascular systems. Changes produced in the electrocardiogram are interpreted as being due to toxic effects on the heart muscle. These observations are in contrast to those of Peters and Horton (394) who recently reported on 25 normal subjects in whom continuous intravenous administration of histamine was given at rates varying from .0017–0.044 mg. per minute. Although significant changes were seen in the electrocardiogram of 24 of the 25 cases, the effects are considered to be of minor physiologic importance. The most common change reported is the loss or inversion of the T wave. The effect of histamine on this wave disappears within 5 to 15 minutes after injection of the drug is discontinued. Other changes frequently observed are in rate, rhythm, A-V conduction time. Impairment in atrio-conduction is manifest only occasionally. Premature ventricular contractions, flattening of the QRS complex and left axis deviation are not common. The authors contend that no clinical or electro-

cardiographic evidence of permanent cardiac damage resulted in any of the 25 subjects, nor was anginal distress or definite symptoms of coronary insufficiency observed.

DIGESTIVE SYSTEM

a. *Intestinal Activity*

Histamine has a stimulating action on the musculature of the gastrointestinal tract of most animals, the rabbit being a notable exception. In unanaesthetized dogs and cats the intestinal tonus is greatly increased (17). In most anaesthetized animals intravenous injection usually causes marked stimulation, which is diminished but not abolished by atropine (4). Hypodermic injection requires more than four times the intravenous dosage and injection into the intestinal lumen is ineffective with two hundred times the intravenous dose (18). Histamine likewise activates the isolated gall bladder. In the intact animal, however, the response is unpredictable. Lueth, Orndoff, and Ivy (19) observed in man that evacuation of the gall bladder occurs only occasionally after injection of histamine. The occasional contraction is stated to be due to the action of acid from the stomach entering the duodenum rather than to a direct stimulating effect of the drug on the musculature of the bladder.

b. *Gastric Juice*

Histamine activates several of the glands of external secretion, the most responsive being the gastric glands; in fact, histamine is the most potent known excitant of gastric secretion. The mechanism by which the drug stimulates secretion is not known. In case of gastric juice its action is independent of innervation and an isolated gastric pouch responds as readily as normally innervated gastric mucosa. Histamine is effective in doses which have little or no effect on blood pressure. The maximal gastric response to histamine in man occurs in twenty to thirty minutes after a subcutaneous injection, and secretion subsides in one to one and one-half hours. The action is only partially antagonized by atropine. While histamine itself can be extracted from gastric mucosa in sufficient quantities to be effective in stimulating gastric secretion of a second animal,

it is still unknown whether the amine plays a physiological role in the production of gastric juice. An extract of the fundic mucosa of the human stomach contains 10.2 mg. histamine per kg. of mucosa, that of the antral mucosa only 5.8 mg. (20).

The stimulation of gastric secretion by histamine involves both the acid and volume. It is believed by some that gastrin, the secretory-excitant principle of gastric extracts, is probably histamine or a closely related derivative; secretin, the corresponding principle of duodenal extracts may also be related (4). A male subject with a permanent gastric fistula has been studied by Wold and Wolff (21) in an effort to correlate vascular changes in the gastric mucosa with changes in motility and secretion of the organ, direct observation of both the gastric mucosa and a collar of gastric mucosa around the stoma being possible. Histamine administration to this man was attended by an observable increase in blood flow, motility, and acid production.

Histamine acid phosphate and histamine dihydrochloride in beeswax-mineral oil suspension, when given intramuscularly in dogs with Heidenhain pouches, exhibits a prolonged and intense stimulating action (22). The volume of juice obtained is many times greater than that obtained when histamine in comparable amounts is administered in saline solution.

Histamine, when administered subcutaneously to anaesthetized rats in which gastric secretion is continuous, has little if any effect on gastric secretion (23).

Animals with jejunal transplants (pedicle grafts) in the anterior stomach wall fail to respond in the usual manner to the stimulation of gastric secretion by the drug (24). Gastric analysis, made before and after the transplants, reveal the combined and total acidities to be lower in each instance after the transplants. Similar studies have indicated that transplants from the ileum and colon are without effect in the inhibition of the development of an acid pH of the gastric mucosa following histamine; in these studies both duodenal and jejunal grafts were effective (25). The conversion of a gastroenterostomy into a jejunal graft caused a reversal of the normal response to histamine in five of six animals (26).

c. *Other Secretions*

Histamine also has a slight stimulating action on salivary, pancreatic, intestinal and lacrimal secretions but the action is relatively brief in duration and the effects appear complex. The mechanism of these actions is unknown but it has been observed that atropine inhibits the response in the submaxillary but not in the parotid gland. The effect is not marked in man. Salivary secretion of experimental animals is stimulated only when comparatively large doses are given. Part of the increased output is only apparent as some of the saliva appears to be pressed out of the alveoli and ducts by muscular action. The true stimulating effect does not depend on an increase in blood flow through the glands, for the secretory response far outlasts the circulatory response. The action may be linked with the cholinergic innervation of the gland inasmuch as the response can be augmented by eserine and abolished by atropine (27). In case of the submaxillary gland, saliva stimulated by histamine has a richer organic content and a lower ash than that of chorda tympani stimulation (4).

A number of drugs counteracting the action of histamine on the intestinal motility and gastric secretion are discussed in Part II.

Uterus

One of the most characteristic actions of histamine is the powerful contraction of the isolated or intact uterus. This effect on the excised guinea pig uterus can be detected in a dilution of 1:150,000,000. The uterus of cats and rabbits is less sensitive, and that of the rat is relaxed. The stimulating action seems to be a direct one on the myometrium since it occurs in denervated tissues. The human uterus reacts readily to histamine at term and postpartum when 0.5–2 mg. promptly produces spasmodic contractions lasting for about thirty minutes. Practical use of this action is excluded by various undesirable side-actions of the drug.

Lungs

Histamine is a powerful activator of bronchiolar musculature, as can be easily demonstrated on the isolated perfused

lung. The action is independent of nerves and is usually unaltered by atropine. Certain animals are much more sensitive to the drug than others. Death by asphyxiation, chiefly as a result of bronchiolar constriction, occurs in guinea pigs with doses as small as 0.1 mg. Bronchial spasm also occurs in man under certain conditions following the administration of large doses. Weiss, Robb, and Ellis (28) reported that the drug has little effect on bronchioles of normal individuals but marked effect in individuals with bronchitis, bronchial asthma, emphysema, and cardiac asthma. The violent dyspnea frequently following intravenous injection of histamine is only partly due to obstruction of the bronchioles through spasm of the muscles; congestion and edema of the mucosa play an important part also. The bronchiolar spasm is antagonized by epinephrine and atropine.

Miscellaneous Effects

The excised ureter is activated by weak solutions of histamine and depressed by more concentrated ones. The urinary bladder is non-responsive. Injection of histamine into the carotid artery dilates the pupil of dogs and cats but constricts it in rabbits (4). Urinary formation is decreased by hypodermic or intravenous injection because of a fall in filtration pressure. In the perfused kidney small concentrations of histamine cause constriction of the vessels, in the perfused intestine dilatation. In the intact animal, histamine produces hyperglycaemia; this effect is probably through the adrenals which liberate epinephrine (29). Histamine also activates carbonic anhydrase, an action which is prevented by low concentrations of zinc (30).

Histamine and Basal Metabolism. Grab (395) in 1929 reported that histamine injected subcutaneously into human subjects produces an 8 to 15 per cent increase in basal oxygen consumption. In the same year Knipping and Stiger (396) found a marked elevation in basal metabolism after subcutaneous injection of 15 to 30 mgm. of histamine. A year later von Euler and Liljestrand (397) observed that 0.4–0.7 mgm. of histamine phosphate injected subcutaneously into a trained person produces a small (7 per cent) rise in metabolism.

Dzsinich and Pely (398) in 1934 obtained equivocal results in 17 human subjects given 1 mg. each of histamine subcutaneously. Eleven showed a decrease in basal metabolism, 6 were within experimental limits. It should be noted that the metabolic tests in this series of observations were made some hours after the time of injection.

The first investigators to demonstrate a metabolic effect of intravenously injected histamine on human subjects were Weiss, Robb, and Ellis (28). These workers found an elevation of as much as 50 per cent in the oxygen consumption of some cases. The recent results of Peters, Horton, and Boothby (399), 1945, are consistent with these observations. The latter group found that the increased oxygen utilization during intravenous injection is roughly proportional to the rate at which histamine is given. This effect ceases soon after administration is stopped. The reason for the increased oxygen consumption is not stated. The reviewer would suggest a possible relationship with epinephrine, which is liberated when the blood pressure falls.

TOXICOLOGY

a. *Animals*

Excessive amounts of injected drug may be followed by death in a few minutes in many animals, yet certain species, such as the rat and mouse, are extraordinarily resistant to histamine. Although the histamine content of their organs does not differ significantly from those of the very susceptible guinea pig, rabbit and dog (31), mice and rats are ten or more times less susceptible than these (32). While most animals succumb as the result of asphyxia, with the lungs greatly distended, severe symptoms in the rabbit arise from constriction of the pulmonary arterioles which causes circulatory failure.

Using increasing doses of histamine dihydrochloride suspended in a cottonseed oil-Falba base, Hueper and Ichniowski (33) were able to produce a standardized and graded shock in dogs. They observed that marked hemoconcentration is not a characteristic hematic manifestation in many of the dogs. The plasma viscosity decreases only slightly or moderately during

shock, while the colloid osmotic pressure of the serum increases considerably. These authors believe that early deaths during histamine shock are practically always cardiac deaths, while animals with delayed deaths exhibit manifestations associated with increased capillary permeability.

b. *Clinical Symptoms*

A concentration of 1:20,000,000,000 in circulating blood produces recognizable effects (4). Intravenous injection of 0.5–1.0 mg. causes momentary flushing of the face succeeded by pallor, metallic taste, faintness, frontal headache and rapid pulse. The headache lasts several hours, the other effects thirty minutes or less. Serious histamine intoxication in man rarely occurs. When it does, it is usually the result of an error in dosage or substitution of the drug for ergot in obstetrics. The symptoms are stated to be more alarming than dangerous (34). Subcutaneous injections of 2 to 4 mgm. causes swelling and infiltration of the tissues with itching and pain. The face, head and conjunctiva become conjested; generalized vasodilation with a rise in skin temperature, fall in blood pressure, intense headache and depression follow. Larger doses produce a precipitous drop in blood pressure, visual disturbances, bronchial constriction, dyspnea, vomiting, and coughing of viscus mucous, diarrhea and, in severe cases, shock. Since epinephrine is a specific physiological antagonist to the drug, it will counteract the symptoms if administered sufficiently soon. In cases of shock a restoration of normal blood volume is necessary.

Histamine Absorption, Metabolism, and Excretion

Histamine is rapidly absorbed from all sites when administered hypodermically. It is usually inactive or only slightly active when taken orally. Very little of the drug can be recovered in the urine as most of it appears to be destroyed or bound within the body. Continuous intravenous injection in man at constant rate maintains uniform effects for some time, so that histamine must be inactivated as fast as injected. Histamine injected intravenously into a rat disappears from the blood within fifteen minutes. The highest concentration of tissue histamine is then found in the kidneys. Rose and Browne

(35) claim that after removal of the adrenal glands the rate of disappearance from the blood and tissues is diminished. Steggerda, Essex, and Mann (36) have found that most organs are capable of removing or destroying histamine; the kidneys are the most active, then the liver, heart, lungs, hind limbs and intestines.

There are probably several mechanisms operating in its destruction. A chemical process, possibly deaminization with subsequent oxidation, is supposed to account for the rapid detoxification of parenterally injected histamine. That simple capture of histamine by the tissues, particularly of the lung, contributes largely to the removal of histamine is the opinion of Ahlmark *et al.* (37). Rocha e Silva (38) has recently suggested that this capture is due to chemical combination with free –COOH groups of cell amino acids. Another mechanism, which is considered especially with the fate of histamine in the gastrointestinal tract, has long interested investigators. The oral ingestion of histamine in doses which would be toxic if injected causes few or no significant symptoms. Doses as large as 225 mg. for man and 300 mg. for the guinea pig are tolerated by mouth without toxic effect, although 1 mg. by vein produces striking symptoms. Furthermore, appreciable amounts of the amine are continually being formed in the intestine (39). Best (39) and Best and McHenry (40) found an enzyme, histaminase, present in various animal tissues which is capable of destroying histamine. It is present in highest concentrations in the intestinal mucosa and in the kidney, facts which may account for 1) the lack of effectiveness of orally administered histamine, and 2) the absence of, or traces only of, histamine in the urine.

Histaminase, possessing the characteristic properties of an enzyme, is inactivated by peptic digestion and heat. Its action is slow and several hours are required in vitro before destruction of the substrate can be demonstrated. For this reason there is doubt as to its exact role in detoxifying histamine in the animal body. So slow is the action that many hours are necessary for assay of its activity. One unit of the enzyme is the amount required to inactivate one mgm. of histamine in one day. The enzyme has been used in experimental anaphylaxis

and in treatment of various allergic conditions but results have been doubtful. (See Part II.) There is little evidence at present that endogenous histaminase actually destroys histamine formed within the gastrointestinal tract or that it constitutes one of several mechanisms possessed by the body for inactivation of absorbed or liberated histamine.

According to Anrep *et al.*, 1944 (41), histamine is eliminated in the urine in a conjugated and a free form. In the rabbit, in which the blood histamine is high, very little histamine is excreted; in the cat, in which blood histamine is extremely low, the histamine of the urine may be as high as 15 μg./cc. Carnivora and Herbivora differ not only in respect to the concentration of histamine excreted but also the form in which it is excreted. In Carnivora almost the entire histamine (98–100%) is excreted in the conjugated form, while in the Herbivora most of it is free. In the rat both forms are present in varying proportions. Administration of meat leads to a considerable excretion of conjugated histamine. Orally administered histamine is eliminated in a conjugated form to the extent of about 5% of the amount administered. Injected histamine is eliminated in traces only and in the free form.

Quantitative Estimation of Histamine in the Blood and Tissues

Best and McHenry, 1930 (40), determined the histamine content of various tissues by preliminary treatment with hot HCl, removal of acid by drying in vacuo and distillation with alcohol, extraction of the filtrate with water, neutralization, filtration, and finally estimation of the filtrate on the blood pressure of the etherized cat. Dog's blood treated in this manner was found to contain 0.4 mg. of histamine per Kg. blood. Rose and Browne (42) later modified the method for studies on all tissues.

Claiming that the frequent failure of attempts to detect histamine in normal blood is due to use of extracts containing other substances which obscure the action of the histamine, Barsoum and Gaddum (43) developed a method using the following steps: 1) precipitation with trichloracetic acid followed by filtration, 2) removal of the trichloracetic acid from

the filtrate with ether, 3) hydrolysis of the filtrate with HCl and subsequent removal of excess acid by drying in vacuo and distillation with alcohol, 4) extraction of the residue with hot alcohol saturated with NaCl, filtration and removal of the alcohol from the filtrate, 5) extraction of dried residue with water, neutralization to litmus, and pharmacological assay on guinea-pig intestine.

Code (44, 45) modified and shortened the above method, the important steps being: 1) treatment of the blood with trichloracetic acid and, after standing for one-half to one hour, filtration by suction, 2) digestion with concentrated HCl for ninety minutes, removal of acid by repeated treatment with alcohol, 3) extraction of dried residue, neutralization, and assay on the intestine or uterus of the guinea pig, or on the blood pressure of the cat. Schild (46) has described a quantitative assay for histamine from the contractions of isolated gut of the guinea pig. Based upon the linear relation between log-dose and response for each section of gut, his procedure gives a precise method of estimating the histamine potency of an extract.

Attempts to demonstrate the presence of histamine in normal urine by biological methods were, until recently, quite unsuccessful. Anrep *et al.* (41) claim that histamine is normally excreted in a conjugated and inactive form from which the active base can be released by hydrolysis. Conjugated histamine, like the free base, is readily absorbed from the urine by charcoal (B.D.H. decolorizing charcoal) from which it is released by repeated washing with acidulated alcohol. A large amount of conjugated histamine can be thus collected on a relatively small amount of the adsorbent. The eluate is almost free of the organic substances of the urine. The method developed by Anrep and co-workers for the quantitative estimation of urine histamine is too involved to be reviewed here.

Liberation from Tissues—General

While histamine can be extracted from most tissues in varying amount, its liberation under various physiological and pathological conditions can be demonstrated. The process of blood coagulation is associated with liberation of the amine and

one or more substances which contract various types of smooth muscle (47, 48). When perfused tissues, particularly the rabbit's ear, are used for the purpose of detecting special vasoconstrictor substances in the circulating blood, it is imperative to prevent coagulation. "Pre-heparinization" of the donor animal is required if the tone of the vessels of the perfused ear is to be reasonably low (49). According to Landis *et al.* (50), serum is completely unsatisfactory for such assays in the rabbit's ear. Kellaway and Rawlinson (51) have shown that histamine is liberated during protracted saline perfusion of various isolated organs, particularly the lung which is said to yield histamine at 43° C.; vigorous ventilation even with oxygen increases the histamine output. After about seven hours of perfusion of the isolated liver of the cat with saline at 38° C., histamine, inorganic phosphate, alkaline phosphatase, catalase, esterase, and proleolytic enzymes begin to appear in the perfusate; this is indicative of cell damage. From the perfused hind limbs of the guinea pig, histamine is liberated at temperatures between 45° and 50° C.

Anrep, Barsoum, *et al.*, 1935 (52), 1939 (53), found that the concentration of histamine in the venous blood of skeletal muscles increases during exercise proportionally to activity. Heart muscle liberates it continuously and proportionally to its activity (54). Ambache and Barsoum (55) found histamine to be released during the active contraction of smooth muscle induced by acetylcholine, potassium chloride or pituitary extract.

Confirming and extending their previous findings on animals, particularly the dog, Anrep *et al.*, 1944 (47), observed that conditions accompanied by a relatively deficient circulation in man lead to a liberation of measurable amounts of histamine. During the period of increased blood flow following ischemia, the histamine containing blood is greatly diluted with fresh blood and is rapidly washed out of the limb. The histamine equivalent returns to normal with the first minute of reactive hyperemia. Vigorous muscular contraction of short duration is accompanied in man, as in the dog, by a release of histamine which is considerably larger than that following arterial occlusion or venous congestion. In all these

conditions there is a relative local deficiency of circulation. The liberated histamine is considered one of the factors concerned in the readjustment of balance between the metabolic requirements of the tissues and their blood supply.

Eichler *et al.* (56) found a tremendous though transitory increase in the histamine content of blood plasma in cats breathing 10 per cent oxygen (equivalent to 18,000 feet); the curve showed a rise from a normal of 0.056 to 0.12 to levels as high as 480 μg. per cc. in the first ten minutes, maintenance of the high level for about thirty minutes, and return to normal within an hour. The significance of these changes has not been stated.

Kwiatkowski (57) reports that a substance pharmacologically indistinguishable from histamine can be extracted from nerves, and that the resulting extracts are inactivated by histaminase. Nerves producing antidromic vasodilation have a high histamine content, and stimulation of their cut dorsal roots results in the liberation of a histamine-like substance into the venous blood. Lambert and Rosenthal (58) describe the liberation of histamine in skin on stimulation of the splanchnic nerve. Kwiatkowski suggests that histaminergic nerves exist as well as cholinergic and adrenergic nerves.

The liberation of histamine by peptone has been a subject of controversy for 30 or more years. Dale and Laidlaw, 1910 (59), in their early paper on the pharmacological properties of histamine pointed out the similarity between its effects and those of intravenous peptone. Abel and Kubota, 1919 (60), argued that this might be due to contamination of the peptone preparations with histamine. Although some preparations contain rather large amounts of histamine, as was shown by Hanke and Koessler (61), the familiar actions of peptone are still attributed to the properties of peptone itself (Hanke and Koessler, 1920 (61); Abel and Geiling, 1924 (62); Clark, 1926 (63)). Lewis, 1927 (64), showed that peptone, punctured into the human skin, produces the characteristic triple response and concluded that it acts by the liberation of histamine as in anaphylaxis. He also suggested that the liberation of histamine by peptone is due to cell injury. More direct evidence for this view was put forward in 1937 by Feldberg, Kellaway and

O'Connor (66), who found that peptone causes an output of histamine from perfused guinea pig's and cat's lungs.

Ungar, 1944 (67), has found that blood cells of normal rabbits, guinea pigs, and rats, when mixed in vitro with peptone, liberates histamine into the plasma. The amount of histamine so released from the blood of animals previously subjected to trauma, adrenalin, local anaesthetics and ascorbic acid is reduced.

The release of histamine in vitro from blood cells of sensitized dogs, guinea pigs, and rabbits whose blood was incubated with antigen, has been reported by Katz (68). These findings were confirmed on rabbit's blood by Dragstedt *et al.* (69). Further work by Katz (70) has shown that the greater part of the histamine comes from the white cells, but that red cells, too, contribute to this release in "in vitro" shock. The presence of plasma is not essential for this phenomenon, thus, sensitized blood cells release histamine when washed and suspended in Locke's solution containing antigen. At 37° C. the greater part of the release takes place within two minutes and is completed within seven minutes. The minimal antigen (crystalline egg albumin) concentration giving a maximal release is around 1:1000, the minimal concentration occasionally giving a detectable release is around 1:250,000. Blood cells from animals sensitized up to 100 days previous to the experiment release histamine in "in vitro" shock. If it be true that the life span of blood cells is below this period, this would mean that cells can become sensitized without necessarily having been in contact with the antigen. In experiments on rabbits' blood, the appearance of an active principle besides histamine is occasionally observed. This substance does not stimulate the isolated, atropinized guinea pig's ileum; it lowers the atropinized cat's blood pressure and causes an epinephrine secretion in cats (70).

The Implication of Histamine in Certain Physiological and Pathological Processes

Because few other chemical constituents of the body have such a diversity of action as histamine, this chemical has provided the basis for innumerable theories of poorly understood

physiological and pathological processes. Over production and liberation of the chemical has been offered as an explanation for a variety of conditions too numerous to discuss in detail in this review.

Surgical Shock

Histamine has been implicated as a causative factor in surgical shock. During World War I the French surgeons Quenu (71) and Delbet (72) concluded that shock following extensive injury is due to the absorption of a depressant substance from damaged tissue. The experimental work of Bayliss (73) and Cannon (74) appeared to support this contention. The work of the latter investigators showed that shock can be produced experimentally in animals by trauma to the limbs, etc., and that the syndrome occurs readily whether the injured area is denervated or not, leading these workers to conclude that nervous influences are not significant. They showed, however, that shock does not occur when the circulation through the injured limb is interrupted. They inferred from this that some tissue toxin is absorbed and distributed into the general circulation from the injured area. With the identification of histamine as a normal constituent of tissues and with the demonstration that histamine produces a shock state resembling that following extensive injury, it was reasonable to assume that histamine is the cause of surgical shock. Direct evidence implicating histamine in surgical shock has not been obtained, however, and in the past ten years evidence has been presented which indicates that other factors (particularly, a critical reduction of blood volume due to loss of fluid) are adequate to account for all the manifestations of shock.

Headache and Histamine

Wolff (75, 76) discusses the mechanisms of headache in two articles which summarize the results of his previous work. He presents evidence that, whereas headache following histamine injection is produced by traction on the cerebral arteries at the base of the brain as they dilate, migraine is the result of changes in extracerebral arteries. The former is relieved by

increase of intracranial pressure, which thereby furnishes support for the distended arteries, while relief from migraine is not so obtained.

Horton (77) has found that in many subjects susceptible to headaches, typical attacks of unilateral pain can be induced by the subcutaneous injection of 0.1 to 1.2 mg. of histamine. Patients with spontaneous headache are unable to distinguish between spontaneous and histamine induced pain; the two seem identical. When attacks are induced by the subcutaneous injection of histamine and the patients are under controlled environmental conditions, it can be demonstrated by electric thermocouples that, as the attack comes on, the surface temperature of the involved side of the head rises more rapidly and to a higher level than that of the opposite side. According to Horton, it is never possible to induce attacks of this character in normal subjects by giving a similar amount of histamine. When epinephrine (1:400,000 solution) is given to patients having either induced or spontaneous attacks, relief from pain is prompt.

Dragstedt (78) has indicated other conditions in which histamine has been accused of having a prominent role. Since histamine causes a lowering of the blood pressure, and since it is formed in relatively large amounts in the intestine, it has been held by some to be a causative factor in the low blood pressure syndrome of patients. Histamine, curiously enough, has also been accused by some as being a causative factor in hypertension, the basis for this accusation being that one of the interesting pharmacological characteristics of the substance is its stimulating action on the adrenal glands with the subsequent secretion of epinephrine. Having a powerful stimulating action on gastric secretion, histamines has been indicated as a causative factor in the development of peptic ulcer. It also has been accused of being responsible for the toxemias of pregnancy. Since it is also a powerful stimulant to uterine contraction, it has been held to be the cause of the onset of labor. Direct evidence to substantiate these claims is not available, excepting, perhaps, in peptic ulcer.

In summing up the indictment against histamine, Dragstedt makes the following interesting statement: "It is thus seen

that what was initially of interest to chemists only, came to be a subject of great interest to pharmacologists, pathologists, immunologists, surgeons, obstetricians, etc. It may also be said that like some notorious gangster who is seized in every dragnet when a high crime against society has been committed, that histamine has likewise been before the bar of judgment upon innumerable occasions and somehow has usually managed to escape."

There are, however, several indictments against histamine which have not been dismissed. It is still charged with the production of symptoms of anaphylactic shock and allergy.

The Role of Histamine in Anaphylactic Reactions

Concurrently with the accumulation of a great variety of experimental observations on conditions under which anaphylaxis occurs, several theories explaining the manifestations have been elaborated. Much evidence has been presented to support a humoral concept, namely, the intravascular formation of toxins which in turn produce the symptoms.

Vaughn and Wheeler (79) demonstrated that from almost any protein a highly toxic substance can be produced by cleavage under suitable conditions and that this substance produces effects in animals closely resembling the symptoms of anaphylaxis. Biedl and Kraus (80) pointed out that intravenous injection of peptone produces reactions virtually indistinguishable from anaphylactic shock, and Dale and Laidlaw (81) reported that the pharmacological effects of histamine are strikingly similar to those of anaphylaxis. The latter state: "We content ourselves with recording as a point of interest and possible significance, the fact that the immediate symptoms with which an animal responds to an injection of a normally inert protein, to which it has been sensitized, are to large extent those of poisoning by beta-iminazolylmethylamine." Since the publication of these early studies, evidence has accumulated both in favor of and opposed to the idea of the elaboration of a chemical substance, histamine-like in nature, during anaphylactic shock.

Manwaring, in 1910 (82), observed that short-circuiting the liver out of circulation prevents anaphylaxis, an observation

not confirmed years later by Weil (83) and Weil and Eggleston (84), and concluded that the acute anaphylactic reaction in dogs is an explosive autointoxication of hepatic origin, due to the liberation of a depressor substance. Lewis, 1927 (85), wrote that various reactions occurring in the skin in response to intradermal injections appear to be due to the liberation of a histamine-like substance which in turn produces the wheal and other skin reactions. In 1927, Best *et al.* (86) established that living tissue contains histamine and as a result of this observation Dale (87) reaffirmed the anaphylatoxin hypothesis, identifying the toxin as histamine. Dale was careful to point out that the source of the histamine is the tissues themselves and not the antigen or plasma proteins.

Then followed an array of circumstantial evidence which is convincing to all but a few. Dragstedt and Gebauer-Fuelnegg (88) found a smooth muscle stimulating agent in lymph of dogs submitted to anaphylactic shock. Bartosch, Feldberg, and Nagel (89) found that when antigen is perfused through the isolated lungs of sensitized guinea pigs, a histamine-like substance is liberated into the perfusate. Since histamine disappears rapidly from blood, Dragstedt and Mead (90) reexamined a large number of anaphylactic dogs and found histamine regularly in the plasma whenever an appreciable anaphylactic reaction occurred. These workers further contended that the active substance is histamine since it is inactivated by histaminase. Employing the sensitive method of Barsoum and Gaddum (91) for assaying blood histamine, Code (92) confirmed these observations and further found that histamine is liberated in the guinea pig as well as the dog. Code cautiously concluded that the liberation of histamine during anaphylactic shock in the guinea pig and dog does not establish it as a fundamental accompaniment of anaphylaxis. He admitted, however, that the amount of histamine liberated during severe anaphylactic shock in dogs is sufficient to produce the precipitous fall in blood pressure.

Schild (93), 1939, following the early lead of Bartosch, Feldberg, and Nagel, studied a variety of tissues subjected to the assulting dose of antigen and found histamine released into the perfusate. There is then strong evidence to support the view

that the histamine liberated into the blood stream during severe anaphylaxis is derived from the tissues themselves. Code's results indicate that during anaphylaxis in guinea pigs the blood histamine increases from two to thirteen times the control value, while in dogs the increase is from two to eighty times normal. The maximal concentration is usually found to occur within the first ten minutes, after which the content falls rapidly; normal levels are again reached within two to three hours. During the time of maximal concentration, Code observed that 79 to 91 per cent of the whole blood histamine is free in the plasma. Dragstedt *et al.* (94) observed that if the lungs of a sensitized rabbit are perfused with saline to which antigen is added histamine is liberated, the amount released is notably less than that for the guinea pig.

Objections to the Histamine Theory of Anaphylaxis

In discussing the role of histamine in anaphylaxis, Wiggers (95) stated: "To me, many of these arguments are not convincing. The chance is great that some of the differences mentioned are fortuitous rather than of fundamental importance." An earlier objector to the histamine view, Wells (96), pointed out that histamine fails to account for all the phenomena of anaphylaxis since: 1) it fails to desensitize animals or tissues, yet produces strong reactions in the uterine strip that has been thoroughly desensitized; 2) histamine does not produce the temperature reactions usually accompanying anaphylaxis; 3) histamine does not produce the changes in coagulation of the blood usually observed in anaphylaxis; 4) quinine augments the susceptibility of sensitized animals to the foreign protein but does not affect the intoxication produced by histamine. Moreover, Rigler (97) and Daly *et al.* (98) found no appreciable difference in the histamine content of normal and sensitized guinea pigs. Rose and Weil (99) reported that the blood histamine in rabbits is definitely reduced during the anaphylactic reaction and this has been confirmed by Zon *et al.* (100) and Dragstedt *et al.* (101). Code and Hester (102) also observed a decrease in the blood histamine during anaphylactic shock in the horse and calf. In further work with the rabbit, Rose (103) showed that during anaphylactic shock

there occurs a marked decrease in the blood and plasma histamine and a decrease in the histamine content of the lung and spleen. These observations are serious blows to the histamine concept. Some of these objections, however, have been adequately met by more recent findings (see Part II, Recent Advances Regarding the Histamine Problem); others have not, and until they are all satisfactorily answered, the histamine hypothesis cannot take precedence over the cellular theory.

Ratner (104) contends that the histamine liberated during anaphylaxis is merely a concomitant finding representing an end product of marked physiological disturbances, which release it from its normal habitat in the blood and tissues. The increased histamine content of the blood at the height of anaphylaxis may be the result and not the cause of the allergic reaction. It must be conceded, however, that if present in excessively large amounts, it can contribute to the intoxication of the animal.

The adherents of the cellular or antigen antibody theory of anaphylaxis state that one need not invoke a toxic substance such as histamine to account for the disturbed physiology of anaphylaxis. In opposition to adherents of the histamine theory, they believe that the dominant symptoms of anaphylaxis (such as bronchospasm of the guinea pig, circulatory failure of the dog and cardiovascular failure of the rabbit) can all be brought into accordance on the basis of spastic contraction of strategically located smooth muscle.

On the Source of Histamine Released from Tissues During Anaphylaxis

The source of the histamine liberated during anaphylaxis has been determined. The following experiments demonstrate that histamine is released from the shocked tissues and not formed either from the antigen or from the tissue. The histamine content of successive samples of venous perfusate collected from perfused, shocked lungs does not run parallel to the antigen (egg albumen) content of the samples (105). The appearance of histamine in the venous perfusate is associated with a corresponding decrease in histamine content of the tissue as shown by experiments in which one lung is subjected to

shock, while the other is used as a control (106). In two perfused lungs, Schild (107) produced shock with 1 and 10 μg. egg albumen respectively. If all of the albumen histidine had been decarboxylated, it would not have accounted for more than 12 and 16 per cent, respectively, of the histamine found in the perfusate, the maximum histidine content of egg albumen being 2.5 per cent (108). The histidine decarboxylating power of the guinea pig's kidney during sensitization or shock does not vary (109).

Using refined methods, Schild (110, 93) estimated the release of histamine from different tissues. For the aorta it amounted to 3.8 μg. per gm. The release, which is depressed at low temperatures, occurs apparently in two stages: 1) an initial reaction, requiring only a few seconds contact with the antigen and relatively high temperatures, probably represents the actual release from the cells; and 2) a later and slower phase which proceeds at lower temperatures and which might represent the diffusion of released histamine from extracellular spaces into the bath fluid.

The cell is not a diffusion-tight chamber in the interior of which histamine is present in a freely diffusible form (111) and "injury of the cell" cannot be interpreted as damage of an outer cell membrane allowing the histamine to diffuse out. This statement might seem at first view to contradict the fact that grinding up small pieces of tissue in saline solution with silica or sand brings histamine into solution. However, this procedure releases only part of the histamine. Trethewie (111) showed that cells may be divided into small particles which retain their histamine. Samples of dog's liver were ground up with silica in saline solution and centrifuged for a short time. Microscopical examination of the supernatant fluid revealed the presence of some cellular debris which was spun down by further centrifugation and washed. It contained large amounts of histamine which were brought into solution by heating. Feldberg and Kellaway (112) perfused the dog's liver and found that, in the perfusate obtained after an intraportal injection of staphylococcal toxin, there were suspended large amounts of granulated cellular debris, the particles of

which were so small that no circulatory effects were produced when the perfusate was injected intravenously into a cat. The particles, nevertheless, had retained their histamine which was brought into solution and became active when they were coagulated by heating.

Ungar (67) is of the opinion that lung tissue provides the main source of histamine in guinea pig anaphylactic and peptone shock and that blood cells are only of secondary importance.

On the Mechanism of Histamine Storage and Release

The mechanism controlling the storage and release of histamine within the cell is not known. Feldberg (113) assumed that the release of histamine by the antigen in anaphylaxis might be due to activation of cellular proteinases; this he proposed could be accomplished by exclusion of antiproteinases supposedly present in all cells. There are indications in old and recent literature that proteolysis might be responsible for the release of histamine, particularly in anaphylaxis. Thus Friedmann and Isaac, in 1909 (114), showed an increased urine nitrogen following anaphylactic reactions. Similar results were reported by Abderhalden and Pincussohn (115) and Pfeiffer and Mita (116) who observed the appearance of enzymatic products of proteins in the blood of animals subjected to shock; these products of protein hydrolysis were ascribed to the action of ferments mobilized in consequence of the union of the antigen with the antibody. Pfeiffer and Jarisch (117) confirmed these findings and further demonstrated that the ability of the antigen to activate a proteinase in plasma appears very soon during the sensitization period. Jobling and Petersen (118) noticed that specific precipitates can activate plasma trypsin by 1) adsorption or 2) inactivation of plasma antitrypsin.

In recent years, Miller (119) confirmed an increased excretion of nitrogen in dogs following anaphylaxis, and Dragstedt, Wells and Rocha e Silva (120) found that heparin inhibits both the proteolytic action of trypsin and the ability of peptone, trypsin, and antigen of releasing histamine from normal or sensitized blood cells. Since a proteolytic enzyme-like

trypsin can duplicate all the features of anaphylactic shock when injected intravenously (121, 122), an attractive theory of anaphylaxis based on the activation of proteolytic enzymes has been advanced (113, 121, 122, 123).

According to this view, histamine is bound or anchored to the protoplasmic constituents of the cell by forming peptide bonds with the amino acid chain of tissue proteins. Rocha e Silva (125) believes that the peptide bond displays a definite specificity toward proteolytic enzymes of the benzoyl-l. arginine amide type. It is further suggested that most of the histamine present in living cells is bound to arginine or to lysine and that it can be liberated by the action of a ferment displaying the specificity of trypsin. A proteolytic enzyme of the cathepsin system, probably cathepsin II, is considered the most likely enzyme to liberate histamine. This assumption is based on the findings of Fruton, Irving, and Bergmann (126) that the specific substrate for cathepsin II is benzoyl-l. arginine-amide or benzoyl-l. lysine-amide.

On this basis, Rocha e Silva (125) has proposed an interesting theory of the chain of events involved in the liberation of bound histamine from the cell. Two distinct groups of histamine liberating substances are postulated: 1) substances which act indirectly through the endogenous cell enzymes, the cathepsins, and 2) substances such as proteolytic enzymes and animal toxins which act directly by rupturing the peptide linkages of histamine and the amino acids of cell proteins. In accordance with this view, a host of chemical and physical agents might bring about a release of histamine by activation of the cathepsins. How such agents do this is not, of course, known. It is suggested, however, that changes in pH or in concentration of hypothetical antienzymes and activators might accomplish this.

Histaminase

a) *Methods of Extraction and Purification of Histaminase*

Methods for the extraction and purification of histaminase have been published by Best and McHenry (26), McHenry and Gavin (127), Kiese (128), Werle (129), Laskowski (130),

Stephenson (131). An improved method for the partial purification of highly potent histaminase has been described by Laskowski, Lemley, and Keith (132). By this method an average yield of 450 units of histaminase is obtained from 3 kg. of hog kidney cortex. The average activity is 1.5 units per mg. of protein. This partially purified histaminase utilizes 1 atom of oxygen and produces 1 mol. of ammonia per mol. of histamine.

b) *Action of Histaminase in Vitro*

That histaminase inactivates histamine only in presence of oxygen was shown by Best and McHenry (26). This was confirmed by Edlbacher and Zeller (133). Hydrocyanic acid also inhibits the effects of histaminase. Zeller, Schar, and Staehlin (134) have evidence to show that in the inactivation of histamine by the enzyme oxygen is consumed and NH_3 and H_2O_2 are produced. Zeller, Stern, and Wenk (135) report that aldehyde is produced during the histaminase-histamine reaction. The quantity of oxygen necessary for the inactivation of one molecule of histamine was found by Kiese (128) and by Laskowski (130) to depend on the state of purity of the histaminase preparation, the purest preparations catalyzing the consumption of one atom of oxygen per molecule of histamine. Shephenson (131) confirmed these findings recently by using a highly purified preparation of histaminase from hog kidney cortex and observed that, when histaminase acts upon one molecule of an aliphatic diamine, one molecule of ammonia is liberated, one molecule of aldehyde is formed and one atom of oxygen is utilized. Evidence is presented that hydrogen peroxide is also formed during this reaction.

Histaminase acts very slowly in vitro, but there are indications that in vivo its action is accelerated. Serious doubt has already been expressed as to whether this ferment is the only tool employed by the organism to detoxify histamine.

c) *Action of Histaminase in Vivo*

Since the discovery of histaminase by Best and McHenry in 1930 (26), many contradictory statements concerning its activity in vivo have been made. Various attempts to bring

histaminase into general practice as a therapeutic agent in allergic diseases have also been reported by numerous writers, success as well as complete failures having been obtained. A further discussion of this is given in Part II of this review. Positive experimental results (protection against lethal doses of histamine) have been reported by Karady and Browne (136), whose toxic dose of histamine (4 mg. of free base) was injected intraperitoneally into 250 gm. guinea pigs and whose protective dose of histaminase was rated at 3 units. They reported protection in more than 75% of their animals. Alexander and Bottoms (137), Younger, Freedman, and Nungester (138), and Dragstedt (139) were unable to confirm these results. Using considerably greater amounts of more highly purified preparations of histaminase and improved methods, Lemley and Laskowski (140) have recently, 1945, repeated these experiments. The dose of histamine in the experiments was fixed at 1½ times the lethal dose; histaminase was injected directly into the blood stream immediately preceding the administration of histamine. One hundred units of the enzyme, the maximum tolerated dose, gave protection to approximately one-third of the animals receiving the lethal dose of histamine. The authors conclude that histaminase at the present state of purity is still toxic and the dose cannot be increased to the level which will give a safe protection. The amount of histaminase necessary for complete protection for the guinea pig is estimated to be 200 units or more, which is impossible with present preparations. The hope that histaminase might be used as a tool for the investigation of anaphylaxis, therefore, must be postponed until less toxic and more active preparations are obtainable.

Influence of Hormones on Histamine Content of Tissues

Marshall (141) has recently confirmed the observations of Wilson (142) and of Rose and Browne (143) who found that adrenalectomy leads to a significant increase in the histamine content of most tissues. Rose and Browne suggested that the increase of the amine in the tissues of the adrenalectomized rat is due to transference of histamine from the blood, without any increase in the histamine content of the body as a

whole. Wilson, however, showed that the blood histamine is increased in adrenalectomized rabbits, a result which was confirmed for the rat by Marshall. The latter found that the histamine content of the whole body is increased by about 30% after adrenalectomy, representing an increase of over 200 μg. histamine base in a 40 gm. rat. The source of extra histamine present in the adrenal cortical-deficient animal still remains unexplained.

Ungar (67), 1944, observed that the amount of the amine released in vitro by peptone from the blood of animals previously subjected to trauma and certain chemical agents (adrenal cortical extract, adrenalin, local anaesthetics, ascorbic acid) is reduced. Inhibition of histamine release is stated to be transmitted to normal animals by the injection of serum of traumatized animals. The author gives evidence that the inhibitory substance present in the active sera is produced by the pituitary and acts through the adrenals.

Thyroidectomy, according to Gotzl and Dragstedt (144), decreases the histamine content of the skin, liver, and lungs of rats, while feeding thyroid extracts increases the content of the amine in these organs.

Effect of Hormones on Histamine Sensitivity and on Anaphylaxis

Adrenals

The increased susceptibility of adrenalectomized animals to histamine is well known (145–154). While most observers believe that this enhanced sensitivity is due to lack of cortical tissue, Wyman (152), 1928, contends that it is related to a lack of medullary substance. Gottesmann and Perla (153), 1931, were able to demonstrate, however, that repeated injections of large amounts of cortin to adrenalectomized rats raises the resistance of these animals to histamine. This observation was confirmed by Rose (154), 1939; the maintenance dose of cortin is wholly inadequate, however, to restore the ability of the animal to inactivate the amine in a normal manner.

Flashman (155), 1925, reported that adrenalectomized rats show a marked increase in susceptibility to anaphylactic shock,

and concluded that this effect is related to the degree of suprarenal insufficiency. Wyman (156), 1929, confirmed Flashman's observations but contended that the results are due to lack of medullary tissue and not to cortical insufficiency. Most observers, however, agreed that the cortex plays the more significant role in the increased susceptibility to anaphylaxis and to histamine shock.

Hypophysis

The natural resistance to histamine is depressed in completely hypophysectomized rats, in which the minimum lethal doses is one-fifth to one-third that of normal rats (157). The decreased resistance to the amine after hypophysectomy is probably secondary to the atrophic changes in the adrenal cortex resulting from withdrawal of the adrenotropic hormone of the anterior lobe, for repeated injections of large amounts of cortical hormone raises the histamine resistance of hypophysectomized rats. Molomut (158) produced fatal anaphylactic shock in hypophysectomized rats but not in normal animals; the longer the time interval after removal of the gland, the greater is the susceptibility to the shocking dose of protein.

Thyroid

Excision of the thyroid renders guinea pigs resistant to histamine and to anaphylaxis (159). Administration of large amounts of thyroid extract to normal guinea pigs enhances their sensitivity to anaphylaxis (160) and to histamine intoxication (161). Farmer (162) believes that the increased sensitivity to the amine following administration of thyroid extract explains the heightened anaphylactic response in experimental hyperthyroidism.

Parallelism Between Histamine Sensitivity and Anaphylactic Response

Farmer (162) stresses the apparent parallelism between the anaphylactic response of a species and its sensibility to histamine. Species which, like the guinea pig, are highly susceptible to histamine are eminently susceptible to anaphylactic shock; species like the rat are highly resistant to the drug and cannot be made anaphylactic under normal circumstances. The

degree of histamine sensitivity of a species thus appears to determine its anaphylactic response, a point in favor of the humoral concept of anaphylaxis.

Farmer further contends that the degree of histamine sensitivity of a species, and subsequently its anaphylactic response, are determined by its adrenal cortex hormone (or hormones). This contention is based on the following observations in rats and guinea pigs: In rats, a) adrenalectomy, which eliminates the source of cortin, increases this species' susceptibility to histamine poisoning (151) and to anaphylactic shock (155); b) hypophysectomy, which leads to atrophy of the adrenal cortex (163), exerts the same effect on histamine sensitivity (157) and anaphylactic response (158); and c) administration of cortex hormone to adrenalectomized (153) or hypophysectomized (157) rats restores their natural resistance to histamine. In guinea pigs, a) adrenalectomy enhances susceptibility to anaphylactic shock (160), b) administration of adrenal cortex extract diminishes the anaphylactic response of the normal sensitized animal (164). Administration of thyroid extract enhances the susceptibility of guinea pigs to histamine poisoning (161) and to anaphylactic shock (165). A diet deficient in ascorbic acid exerts the same effects in this species (22–25).

Farmer (162) suggests that the enhancement of histamine sensitivity and of anaphylactic response following the administration of thyroid extract (or the feeding of an ascorbic acid deficient diet) is due to a decrease of the cortin content of the adrenals. The reduction of cortin results from a depletion of the cholesterol stores of the adrenals, from which the cortical hormone is probably derived; the decrease of the cholesterol content, in turn, is stated to be due to depletion of the ascorbic acid stores of the adrenals.

PART II: RECENT ADVANCES REGARDING THE HISTAMINE PROBLEM

The purpose of this portion of the review is to appraise the present status of certain aspects of the histamine problem. Recent studies on histamine have dealt chiefly with: 1) its liberation by chemical and physical irritants; 2) its participation in

various diseases, particularly allergy; 3) its diagnostic value; 4) the inhibitory effect of various chemical agents; 5) the therapeutic value of histaminase and histamine.

1. Liberation of Histamine by Chemical and Physical Irritants

a. *Animal Poisons.* Feldberg and Kellaway (170) were the first to point out that lecithinase of certain animal venoms liberates histamine. Thus the lecithinase of bee and snake venoms, when acting on egg yolk, produces a hemolytic substance, lysolecithin, which in turn liberates histamine. Trethwie (171) reported that the hemolytic capacity of several snake venoms runs parallel to the histamine liberating capacity. Rocha e Silva (121) and Arellano, Lawton, and Dragstedt (122) showed that histamine liberation by animal poison can be explained on the basis of proteolytic enzymes present in them. The amine is released from guinea pig lung by trypsin (172). Arellano, Lawton, and Dragstedt (122) also showed that intravenous injection of trypsin in dogs leads to a marked increase in blood histamine. The source of this histamine has been shown to be the liver as 6–10 mgm. of the substance disappears from this gland in animals subjected to trypsin shock. A similar liberation of the chemical from the liver of dogs following anaphylaxis is reported by Ojers, Holmes, and Dragstedt (173). Strangely enough the intravenous injection of trypsin and snake venoms in rabbits results in a reduction of blood histamine (174, 175) rather than a rise. Dragstedt and Rocha e Silva (174) found further that the addition of trypsin to heparinized blood of rabbits leads to the migration of the chemical from cells to plasma. Similar observations have been made in sensitized rabbits given a shocking dose of antigen (99) or in normal rabbits given intravenous peptone (176). When the blood of sensitized rabbits is placed in contact with the antigen in vitro, a diffusion of histamine from cells to plasma also occurs (68, 70, 69, 94, 177). Eichbaum and Rocha e Silva (178) found that the presence of ascorbic acid in high concentrations does not prevent this effect.

b. *Parasitic Infestation.* Hamann (179), 1943, has reported that the histamine content of the blood and tissues of rats and

guinea pigs infected with Trichinella spiralis show a greater variability than controls and a definitely higher mean value for blood histamine.

c. *Inflammation and Irritants.* Rocha e Silva (123) has published a review on the role played by histamine during the first stages of acute inflammatory reaction. Lambert and Rosenthal (58) claim that the chemical is discharged from the skin following application of irritants such as chloroform and xylene. Haas (180) also reports an increase in the histamine content of the skin following application of mustard oil, canthardin, croton oil, turpentine, colchicine, etc. This would explain the results of Bier and Rocha e Silva (181) and Rocha e Silva and Dragstedt (182) who found that concentration of trypan blue in areas of rabbit skin treated with snake and bee venoms, trypsin and various irritants depends upon increased endothelial permeability resulting from released histamine. Inflammatory lesions of the rabbit skin, according to Zon, Ceder, and Crigler (183), have two to ten times as much histamine as normal skin from the same rabbit. The authors correlate this increase of the amine with the accumulation of blood platelets at the site of inflamed tissues. Similar increases of the histamine content in rabbit's skin is reported to follow allergic inflammation (184) and irradiation to ultraviolet light (185).

2. On the Participation of Histamine in Various Disease Reactions

a. *Allergy.* The histamine theory of anaphylaxis and allergy has been the subject of much investigation during recent years. The development of the theory and results of certain pertinent studies on experimental anaphylaxis have already been briefly stated (Part I). It cannot be denied that the significance of histamine in the pathogenesis of symptoms in experimental anaphylaxis and in allergy is still contestable. Ratner (104) maintains that the demonstration of histamine in the blood is merely a concomitant finding resulting from the anaphylactic reaction, and can be regarded as the end product of marked physiological disturbances. In opposition to the humoral theory of anaphylaxis, the adherents of the cellular or antigen-antibody theory contend that the symptoms of allergic

states are the result of contractile changes of strategically located smooth muscle.

Some of the objections which have been leveled at the histamine view of anaphylaxis are: 1) failure of histamine to desensitize the uterus by antigens, yet persistence of sensitivity of the organ to histamine after desensitization by the antigen (186); 2) certain chemicals augment or decrease the susceptibility of sensitized animals to foreign proteins but do not effect the intoxication produced by histamine, Smith (187), 1920, Hill and Martin (188), 1932; 3) histamine does not produce the change in coagulability of the blood usually found in anaphylaxis, Wells (96), 1921; 4) decrease of histamine in the blood in anaphylaxis of the horse and calf, Code and Hester (189), 1939, or rabbit, Rose and Weil (99), 1939, Zon *et al.* (100), 1939, Dragstedt (78), 1940; 5) histamine does not duplicate the vascular reaction of anaphylaxis in the rabbit, Ratner (104), 1943; 6) studies with chemical inhibitors of histamine and anaphylactic reactions indicate that higher doses of the protecting substances are needed for preventing anaphylactic effects than for preventing histamine effects, Landau and Gay (190), 1944; 7) histamine is not released in the specific anaphylactic contraction of a sensitized uterus suspended in a suitable bath, Cloyd and Selle (191), 1945.

Most workers, however, seem to agree that there are no major inconsistencies to the assumption that the fundamental allergic reaction is identical with that of the anaphylactic reaction and that histamine, as one of the by-products of this reaction, is causally related to most of the phenomena. The recent evidence favoring this humoral view was presented in 1941 by Farmer (192), Feldberg (113), and Dragstedt (193) and in 1942 by Rocha e Silva (123). Many of the factors and idiosyncrasies of the anaphylactic syndrome remain unexplained and attempts to influence these conditions of hypersensitivity by neutralizing the effects of histamine (as by creating refractoriness with increasing doses of the compound itself or by histaminase) have given inclusive results. It also appears clear that the cellular discharge of histamine does not account for all the phenomena of anaphylaxis. For example,

proof has been presented by Jacques and Waters (194) that a similar discharge of heparin occurs which accounts for the incoagulability of blood during anaphylactic shock. Nevertheless, the question of the involvement of the chemical is progressing from suspicion and circumstantial evidence to more direct and convincing proof that it plays the fundamental role in the anaphylactic reaction. The majority of workers seem to agree now that the source of the histamine is in the tissues of the sensitized animal and that it is released into the blood and lymph as a consequence of the antigen-antibody reaction initiated by the reinjected antigen.

Cerqua (195) found an increase in blood histamine in asthma. Parrot (196) also reported an increase of three to four times normal in three of four cases of bronchial asthma. Capuani (197) also observed an increase in the blood histamine following asthmatic attacks. Randolph and Rackemann (198) found an average of 45 gamma of the compound per 100 cc. of blood in 20 normal individuals with a range of variation from 19–71 gamma per 100 cc. There was a definite increase of the histamine content of 9 patients with bronchial asthma during the development of symptoms, compared with levels found between attacks. They did not find any significant correlation between eosinophilia and the level of the amine in the blood. This latter finding contrasted with the previous finding of Code and MacDonald (199) who reported cases of eosinophilia with a blood histamine content definitely above the normal range. Rose (103) also studied the variation of the histamine content of the blood in 80 patients with asthma, urticaria, angioneurotic edema, eczema, hay fever, and allergic colitis. In contrast with what occurs in the normal individual, the histamine level in allergic patients shows enormous fluctuations in the course of many months or years. Despite the fact that these variations often bear no relationship with the development of symptoms, they show a marked degree of instability, contrasting with the striking stability of blood histamine in normal individuals.

On the basis of these somewhat contradictory results one is led to conclude that although blood histamine is frequently

elevated during the development of allergic symptoms, it is not always so. In this connection the interesting observation of Rose (200) should be noted. This observer reported that while the histamine content of patients with dermatographism usually increases after application of a stimulus, there is frequently a definite lowering below the normal mark within twenty or thirty minutes. Rose did not miss the opportunity to compare this lowering of the histamine content of the blood after exposure to skin irritants with results described previously by Rose and Browne (201) of a decreased histamine content following surgical shock. This same decrease of blood histamine occurs in cases of angioneurotic edema following appearance of symptoms (103). The most that can be said from these data, it seems, is that in certain allergic conditions histamine metabolism is disturbed.

It is possible, therefore, that the somewhat discordant results described by the various workers on the estimation of histamine in the blood of allergic patients may be due to its transient nature in the blood stream. (See Fate of Histamine, Part I.) The findings appear to justify the conclusions that blood histamine of allergic individuals is considerably more labile than that of the normal and that the liberation of the chemical frequently follows the onset of allergic symptoms.

Evidence of a more definite nature for the release of the amine during the anaphylactoid reaction was shown by Katz and Cohen (202). Using heparinized blood collected from patients with pollen and dust allergies, these observers found a definite shift of the compound from the blood cells to the plasma when extracts of the respective allergens were added. The magnitude of increase ranges from a minimum of 60–76 per cent in some cases to 168–900 per cent in most cases. Katz (203), using a cleverly devised method, has recently shown that histamine is liberated from the skin of allergic individuals when extracts of the offending allergen enter in contact with the lower layers of the skin, the epidermal layers of which had been previously removed by a special technique.

b. *Physical Allergy.* A finger of suspicion is being pointed to histamine as the causative agent of the so-called physical

allergies. In certain hypersensitive individuals, an increased liberation of the chemical by physical agents seems to have been well established. Kalk (204) reports that subjects exhibiting dermatographia and other forms of physical sensitivity frequently show an increased secretion of hydrochloric acid of the stomach following application of the stimulus. Horton, Brown, and Roth (205) describe the reaction of patients sensitive to cold and stress the conspicuous analogy between local and systemic reactions to cold and the symptoms elicited by injected histamine. An increased secretion of free hydrochloric acid in the stomach of patients sensitive to cold following immersion of one hand in cold water is also reported (206, 207). Rose (200) observed a definite increase in blood histamine in five of ten patients with dermatographia and in two of three patients with cold allergy following wheal formation after the application of cold.

Capps and Young (208) reported an increase in the blood histamine of a patient with photosensitivity following exposure to ultraviolet light.

Code and MacDonald (199) reported cases of eosinophilia with a blood histamine content considerably above the normal range. Rose (200) also observed an increase of histamine content of the blood of some patients with eosinophilia, while in other patients showing the same symptoms the blood histamine was definitely below normal. Nor could Randolph and Rackermann (198) find a significant correlation between eosinophilia and the histamine level of the blood. In five of eight cases studied by the latter workers the eosinophile counts were conspicuously higher than those reported by Code and MacDonald, nevertheless, there was no increase of blood histamine above the normal range.

c. *Headache.* As previously pointed out (Part I), there is strong circumstantial evidence to indicate that histamine may be implicated in the production of headache. The chemical is a particularly powerful dilator of arterioles and capillaries of the brain and meninges (34). Pickering (6) found that within a few seconds after the intravenous injection of 0.1 mg. of histamine phosphate in normal subjects the systemic blood

pressure fell and the cerebrospinal fluid pressure rose. While these changes were subsiding and the blood pressure was rising to normal, headache developed. Friedman and Brenner (209) also observed that histamine headache appears as the blood pressure rises after the initial drop. Pickering further showed that the headache might be relieved by either raising the intracraneal pressure or by abruptly lowering the blood pressure.

Reference has already been made to the observations of Wolff and co-workers (75, 76, 210, 211, 212). It will be recalled that these workers concluded that histamine headache is the result of a stretching and dilatation of the pial and dural arteries and their surrounding tissues. These authors expressed the belief that the vessels chiefly responsible for histamine headache are the cerebral arteries, particularly the larger ones at the base of the brain, and that the extracranial and dural arteries play a minor role in contributing to the pain of this form of headache.

In this connection the observation of Clark *et al.* (213) that in a certain subject after the injection of histamine, which caused headache, the distortion of the intracranial vessels was nearly twice that following another dilator agent (carbon dioxide) which caused no headache. Northfield (214), too, stated that histamine headache depends primarily on an alteration in the caliber and tension of the blood vessels. He found that histamine injected into the internal carotid artery, but not the external carotid, produced homolateral headache.

Von Storch (215) attempted to determine the minimum dose of histamine, injected intravenously into 74 patients, which would cause headache. He observed that patients with migraine were most susceptible, that patients with chronically recurring headaches of other sorts were somewhat less so and that patients who rarely or never had headache were least susceptible. The headaches produced were all bilateral, although in a few patients with migraine the pain was worse on the side of the usual hemicrania.

Horton (77) reported that in 35 of 72 subjects susceptible to headaches, typical attacks of unilateral pain were induced by the subcutaneous injection of 0.1 to 1.2 mg. of histamine.

When attacks were induced by subcutaneous administration of the drug and the patients were studied under carefully controlled conditions, it was found that as the attacks came on the surface temperature of the involved side of the head rose more rapidly and to a higher degree than that of the corresponding side. A significant observation is that patients with spontaneous headache were unable to distinguish between the induced and the spontaneous attacks; the two seemed identical.

d. *Meniere's Disease.* Finding that patients with Meniere's disease are extremely sensitive to minute amounts (0.10 mg.) of intradermal histamine, Atkinson (216) contends that the characteristic features of this syndrome are normally due to vascularization, dilatation and increased capillary permeability of the labyrinth. The latter changes are thought to be the result of released histamine.

e. *Production of Gastric and Duodenal Ulcers by Histamine.* Repeated injection of large doses (2–10 mg.) of histamine into laboratory animals produces acute gastric ulcers (217, 218, 219, 220, 221, 222, 223, 224), similar to those resulting from pilocarpine. Such ulcers probably result from trauma by either strong peristalsis or increased gastric secretion, or both. The lesions are more easily developed if the animals are fasted (217, 218) or if the liver is previously injured by chloroform or phosphorus (222). The importance of acid in the genesis of ulcer has received support by the experiments of Hay and associates (223), who produced both gastric and duodenal ulcers in a number of laboratory animals (cats, dogs, guinea pigs, ducks, monkeys, calves, and other animals) by intramuscular administration of histamine in beeswax. Administered in this manner, histamine produces tremendous amounts of hydrochloric acid secretion in gastric pouches of dogs. The continuous flow of free hydrochloric acid for long periods of time is suggested by Hay and associates (223) to be the initiating factor in ulcer formation following administration of the compound.

Clinical observations also indicate that histamine might be involved in the etiology of ulcers. Horton (224) reports a direct relation between acute duodenal ulcer with crater formation and histaminic cephalgia. In 10 cases observed in one

year, the formation of ulcer in each instance was secondary to attacks of histaminic cephalgia. During such attacks the gastric acids rise to an abnormally high level just as they would if the patient had received histamine subcutaneously. Horton states that such patients are unusually sensitive to the amine, so much so, in fact, that 0.01 mg. of histamine base is sufficient in many instances to precipitate a rise in gastric acidity equal to that occurring among normal subjects following the subcutaneous administration of .35 mg. of histamine base. More remarkable, however, is the claim by Horton (224) that desensitization to histamine by repeated injections of small amounts of the amine, not only relieved the cephalgia but healed the ulcers within two weeks.

These two contrasting statements concerning histamine and ulcers stimulated the reporting by McHardy and Browne (225) of 2 cases of duodenal ulcer which followed histamine desensitization for migraine headache and vertigo by subcutaneous administration of histamine diphosphate. These observers also report that in a group of duodenal ulcer cases sensitive to histamine and refractory to ordinary medical measures, attempts were made at histamine desensitization; distressing accentuation of ulcer symptoms resulted. Interestingly enough, one patient insisted that while the histamine was giving excellent relief of her vertigo she had to refuse further treatment because of the progressive accentuation of her digestive discomfort.

f. *Histamine Metabolism in Pathological Pregnancy.* Kapeller and Adler (226) have confirmed their previous observations (227, 228, 229) that large amounts of histidine (15–50 mgm. per cent) and only traces of histamine are found in the urine of normal pregnancy in various stages of gestation. Their findings in patients with complicated pregnancy show a difference between toxemic and non-toxemic cases. In the latter group the histidine and histamine excretions are normal. The toxic cases are divided into two groups. In one, containing cases of hyperemesis gravidarum and mild preclamptic toxemia, histidine excretion is normal or slightly reduced and histamine excretion is greatly increased; in the other, containing cases of severe pre-eclamptic toxemia and eclampsia, histi-

dine and histamine are either present in the urine in traces only or are lacking altogether.

Commenting on the way in which histamine might arise in the metabolism of pregnant women, the authors make several suggestions. In normal as well as in toxemic pregnancy histamine is probably formed from histidine, present in large amounts, by the activity of the enzyme histidine decarboxylase. In normal pregnancy most of the histamine formed is destroyed, presumably by histaminase; only traces of histamine escape into the urine. It is suggested that in mild toxemic pregnancy, as in hyperemesis gravidarum, and in mild pre-eclamptic toxemia, the activity of histaminase is impaired and more histamine thus escapes destructive breakdown, resulting in various kinds of intoxication; a large amount of histamine, however, is eliminated in the urine. In severe cases of pre-eclamptic toxemia and in eclampsia a condition may arise in which the activity of the histidine decarboxylase is increased whereas that of histaminase is completely inhibited; the result is that the whole of the histidine appearing in the metabolism is converted into histamine which may cause considerable damage to the vital organs, especially to the liver and kidneys. In consequence, the damaged kidneys lose the power of excreting histidine and histamine which may then be completely retained in the tissues. A vicious circle may thus be caused with the result that as more and more histamine is formed the less active becomes the histaminase because of the arising anoxaemia. Eventually the whole body is flooded by histamine. From these considerations it is obvious that the authors believe that toxemia of pregnancy is due, at least partly, to a disturbance of the metabolism of enzymes responsible for the formation and destruction of histamine.

Tentative support for this suggestion is claimed from the recent works of Marcou (230), Werle (231), and Zeller (232), who report independently on the inability of the serum of toxic pregnant women to destroy histamine. Zeller goes so far as to assume that the activity of the histaminase is diminished or even lacking in the serum of patients with hyperemesis gravidarum, in whose urine Kapeller and Adler find large amounts of histamine.

g. *Miscellaneous.* Lewis (233) has found that the blood serum of urticarial patients causes typical urticarial wheals when injected intradermally into normal subjects. The active material is supposed to be histamine. Investigating the possibility of histamine intoxication as a basis for metabolic disturbances in schizophrenia, Den Hartog Jager (234) was unable to find significant difference between the histamine content of the blood of schizophrenics and that of normals.

3. Diagnostic Value of Histamine

Intracutaneous, subcutaneous and intravascular injections of small amounts of the drug have been used for various diagnostic purposes but in some instances with doubtful value.

a. *Skin reactions in icterus, in conditions of inadequate circulation and impaired peripheral nerves.* Histamine wheals bring out the yellow color of the skin in latent icterus (235). The urticarial response is diminished if the arterial blood supply is decreased, as in arteriosclerosis or Buerger's disease (236). Since the wheal depends upon an adequate circulation of blood, the urticarial response can be used to determine the level of circulatory competency in an extremity when operation is contemplated for gangrene.

The flare around the periphery of the histamine wheal depends upon the integrity of the axon reflexes, or upon the functional competence of peripheral sensory nerves (34). On condition that the circulation is adequate, the intracutaneous injection of histamine can thus be employed as a test for certain neurological disturbances (237). The method provides a means of: 1) differentiating between hysterical and organic cutaneous anaesthesia, 2) detecting malingerers, 3) following degeneration and regeneration of peripheral sensory nerves, 4) localizing progressive spinal cord lesions involving the dorsal root ganglia, 5) differentiating between peripheral nerve and spinal nerve lesions.

b. *Evaluation of intradermal tests as general indicator of allergy.* Various attempts have been made to correlate the histamine sensitivity of allergic patients and their cutaneous response to allergens, and certain writers have suggested the

use of histamine intradermally as a general indicator of the presence of an allergic disturbance. While there is considerable evidence to show that the manifestations of allergy are due to a release of the amine into affected tissues, the assumption that allergic individuals are more sensitive to histamine than are normals is generally denied. Farmer (238), 1945, has reported results of skin tests on 76 allergic patients in most of whom the offending allergens had been identified. Forty-five had hay fever, fourteen had bronchial asthma, ten vasomotor rhinitis, three urticaria, four angioneurotic edema, one migraine. Farmer concludes that it is not possible to differentiate allergic individuals from non-allergic by use of intradermal histamine tests. Ten years ago, Samter (239) wrote that the susceptibility of the bronchiolar musculature for histamine does not parallel its urticarial action of the skin and that the histamine response of the skin is no way an index to allergic tendencies.

c. *Secretory capacity of the stomach.* Because of its powerful stimulating action on gastric juice, histamine is used clinically to test the secretory capacity of the stomach. It is of value in differentiating between pseudo-achlorhydria, which responds to histamine, and true achlorhydria, which does not respond. The dose employed is 0.25 to 0.5 mgm. It is administered hypodermically in an extremity. Should an unfavorable reaction occur, or if a mistake in dosage has been made, a tourniquet can be applied and thus the rate of absorption controlled to keep the subject symptom-free. Gastric response is maximal in 20 to 30 minutes; secretion diminishes in 60 to 90 minutes.

d. *Blood flow velocity.* Intravenous injection of small amounts of histamine (0.001 mg. per kg. body weight) causes prompt dilatation of the minute vessels of the face. The time required for this response has been used as the index of blood flow velocity (5); it represents incomplete circulation time. Histamine is seldom used for this purpose now as more accurate end-points can be obtained with saccharin, sodium cyanide and other agents.

e. *Histamine cephalgia.* Horton, MacLean, and Craig (240) and Horton (77) state that attacks of histaminic cephalgia, associated with its clinical and laboratory evidence of vasodilatation, can be induced at will by subcutaneous injection of 0.1 mg. histamine base. The diagnostic procedure is now rather widely used.

f. *Meniere's disease.* Atkinson (241) reports that patients with Meniere's disease are unduly sensitive to small (0.01–0.02 mg.) intradermal doses of histamine. He concludes that the characteristic syndrome of this group of patients is produced by a reaction in the labyrinth caused by histamine or a histamine-like substance which presumably causes local vascularization, dilatation and increased capillary permeability.

g. *Reported value in diagnosis of pulmonary tuberculosis.* A subcutaneous injection of 1 cc. of 1:1000 solution of histamine, which causes no respiratory disturbance in normal individuals, is stated by Videla and Lamarque (242) to produce transient moist roles after three to five minutes in 90 per cent of the patients with pulmonary tuberculosis.

4. Inhibition of the Histamine Effects

Since there is much evidence to support the hypothesis that the symptomatology of clinical allergies is due to an antigen-antibody reaction which produces histamine or a histamine-like substance, it is not surprising that symptomatic treatment of allergic conditions has been directed toward the nullification of released histamine. In addition to specific therapy (desensitization or hyposensitization) the problem of relieving allergic symptoms deals mainly with: 1) the discovery of substances which antagonize the histamine effect, and 2) the development of nonspecific methods of desensitization which increase the resistance of the organism to histamine by repeated injections of a small dose of this substance.

Numerous investigators have directed their attention to inhibition of histamine and anaphylactic reactions in isolated organs and in intact animals. In 1932 Hill and Martin (188) listed and discussed more than 160 chemical agents which had been used for this purpose up to that time. None of these was found to have significant or specific therapeutic value.

a. *Amino acids.* Edlbacher, Jucker, and Baur (243) demonstrated that several amino acids—histidine, arginine, and cysteine—inhibit or suppress the histamine contraction of intestinal strips of guinea pigs. Ackermann and Wasmuth (244) confirmed these findings and further succeeded in inhibiting with arginine the reactions of intestinal strips of guinea pigs sensitized to serum (245). This reaction was regarded by Ackermann (246) as proving that histamine is the chemical mediator of the anaphylactic contraction of sensitized structures.

Linneweh (247), 1940, reviewed the accumulated information of these amino acids and summarized their anti-histamine effects as follows: 1) they inhibit the action of histamine not only in the isolated intestine of the guinea pig, but also in the isolated uterus of guinea pigs and rabbits, and in the isolated seminal vesicle of the guinea pig; 2) the adrenalin and acetylcholine effects on these organs are not altered by the amino acids; 3) the effect of pitocin is slightly inhibited by arginine. Confirming most of these findings and demonstrating the inhibitory effect of arginine on the anaphylactic response of sensitized pieces of guinea pig intestine, Linneweh attempted to prevent anaphylactic and histamine shock in the living animal by intraperitoneal injections of arginine monohydrochloride. Although protection was not complete in either case, Linneweh felt that his observations gave promise for a desensitizing therapy.

Landau and Gay (190), 1944, carefully re-examined some of the claims of the different authors. They found that: 1) arginine monohydrochloride and histidine monohydrochloride are capable of preventing or stopping the effect of histamine or antigen on the intestinal strip of guinea pigs; 2) the ileum of a sensitized guinea pig is desensitized by adding the specific antigen even if contraction of the strip is prevented by arginine or histidine; 3) the action of acetylcholine on the intestinal strip is not suppressed by these amino acids but is sometimes weakened; 4) although death from histamine injection can be prevented in guinea pigs by a preceding administration of arginine monohydrochloride, all protected animals have respiratory distress and other symptoms of histamine intoxication;

5) arginine gives no protection against death in anaphylactic shock in doses effective against histamine shock, and in higher doses arginine is highly toxic; 6) arginine in 2 per cent solution has no beneficial effect on intradermal skin reactions by histamine or pollen extracts in patients.

The explanation for the inhibitory effects of histamine on the smooth muscle structure has been the subject of much discussion. Ackermann (246) assumes that the =NH imine group present in arginine and in the imidazol ring of histidine competes with a like =NH group of the imidazol ring of histamine. According to this theory, the imine =NH radical represents the anchoring group for the histamine to the chemical receptors of smooth musculature. Should an excess of either arginine or histidine be previously added to the perfusing bath, the drug has no chance to combine with the saturated chemical receptors and consequently cannot produce its characteristic stimulating effects.

Of considerable interest in this connection is the suggestion of Rocha e Silva (38), 1944, that a definite division exists between the toxic effects of histamine (which depend on the $—NH_2$ amine radical) and its anchoring capacity for cell receptors (depending on the =NH imine radical of the imidazol ring). The possibility of separating these two functions of histamine would theoretically enable one to block that part of the molecule responsible for the pharmacologic effect and, at the same time, keep unchanged the capacity for histamine to anchor upon the chemical cell receptors. Rocha e Silva (248) has been successful in synthesizing five compounds of histamine with amino acids which are said to be as effective in inhibiting histamine effects as are arginine and histidine. Acetyldehydrophenylalanyl-histamine, carbobenzoxy-l.tryosyl-histamine, benzoyl-l.tyrosyl-histamine, acetyl-l.phenylalanyl-histamine, and carbobenzoxyl-l.leucyl-histamine are entirely devoid of pharmacologic activity while still having an uncombined imidazol ring. This means that blocking the $—NH_2$ amine radical through chemical combination with the carboxyl groups of amino acid, destroys the pharmacologic activity of histamine. On the other hand, the imine radical (=NH) of the imidazol

ring is apparently kept free in such compounds, which might indicate that they compete with free histamine in its anchoring capacity upon the cell receptors. Since these compounds display an antihistamine effect on the isolated guinea pig intestine of the same order of magnitude as do certain arginine derivatives and histidine hydrochloride, this assumption has been verified (248).

Rocha e Silva (248) has also presented further evidence which indicates that blocking the α—NH_2 or the —COOH groups, or both, definitely increases the antihistamine effect of arginine compounds. His results lend support to Ackermann's view (246) that the anchoring part of the histamine molecule (haptophorous) is the =NH imine radical of the imidazol ring, and the part responsible for the pharmacological effects (toxophorous) is the lateral chain. The observation of Alles, Wisegarver, and Shull (249) that the pharmacologic activity of the drug is inhibited by introducing methyl groups in α— and 5— (imidazol) positions can be interpreted on this basis, for destruction of histamine activity can be brought about by blocking either its toxophorous or its haptophorous function.

Practical use of arginine and histidine as anti-histamine drugs does not, however, seem likely; the results have been deceiving. In order to counteract the effect of as little as 0.02 to 0.05 gamma of histamine base, Roche e Silva (125) states that 5 to 10 mg. of arginine or 2 to 3 mg. of histidine monohydrochloride has to be added. This ratio, 250,000:1 for the antihistamine effect of arginine, explains the failure of arginine to completely protect guinea pigs against the lethal dose of histamine, as well as the poor antihistamine effect of arginine when tried on intact dogs. On the basis of these findings it seems rather unlikely that arginine might offer any hope for the treatment of allergic diseases; one would have to inject huge and possibly toxic amounts of it to counteract the effects of even small amounts of histamine liberated from the tissues.

b. *Synthetic compounds.* A large number of synthetic products, particularly those compounded in Fourneau's laboratory, have been tested. Staub and associates (406) have found two ethylenediamines, thymoxyethyldiethylamine (929 F) and

N-phenyl-N-ethyl-N'-diethylethylenediamine (1571 F), which are effective in counteracting severe histamine and anaphylactic reactions. Rosenthal and Brown (407) and McVicar and McHenry (408) confirmed the observation that 929 F inhibits histamine action upon the isolated uterine and ileac muscle of the guinea pig. Minard and Rosenthal (409), Rosenthal and Brown (5) confirmed the observations of Staub *et al.* that pretreatment with 929 F prevents severe bronchiospasm and death from anaphylactic shock and from the intravenous injection of lethal doses of histamine. Using Staub's preparation 1571 F, Wilcox and Seegal (250) were able to protect guinea pigs against 6MLD of the amine and 4MLD of antigen. Staub (406) was of the opinion that 1571 F is in some respects a more active antagonist of histamine than 929 F.

Loew and Chickering (251), 1941, and Hallenbeck (252), 1943, found that 929 F does not decrease the gastric secretory response to histamine from Heidenhain pouches in dogs but, to the contrary, definitely increases it. Bourque and Loew (253), 1943, reported that 1571 F reduces gastric secretion after stimulation by both histamine and pilocarpine, but fails to influence the gastric secretory response to a meal in dogs with Heidenhain pouches. Burchell and Varco (254), 1942, found that neither 929 F nor 1571 F affects the secretory response of the Heidenhain pouch-dog to the amine. While Hallenbeck (252) observed that both 929 F and 1571 F inhibited the gastric secretory response to a meal in dogs, the results were not thought to be due to a direct antagonism of these drugs to histamine. A decrease in the motility of the duodenum and upper part of the jejunum by 929 F has been reported (255).

Recently several other compounds possessing antihistamine properties have been reported. Two synthetic substances, 2325RP and 2339RP, have been studied and developed by Halpern (400) in France. Both chemicals have been given clinical trial (401–404). One, 2339RP, N-dimethylaminoethyl N-benzylaniline, is commonly known as "antergan." It is less toxic than 2325RP and apparently is more effective as an antispasmodic than either 929 F or 1571 F. In a small series of cases

the drug was reported to be successful in treatment of serum sickness, hay fever, urticaria, intolerance to barbiturates, migraine and other clinical conditions. No reports on the use of this compound have appeared yet in this country. Compounds of alpha pyridinoethylenediamine have been similarly prepared, studied and reported on by Mayer, Hutter, and Scholz at the Ciba Research Laboratories. Preliminary tests indicate that they have a high antihistamine activity for guinea pigs.

A new and very promising synthetic drug, benadryl, is discussed under section g.

Lehmann and Knoefel (256) report that the diethylaminoethyl ester of 9,10-dihydroanthracene-9-carboxylic acid is outstanding for its powerful histamine antagonizing action on smooth muscle (ileum, bronchioles and blood vessels). Using a large series of dogs, Hueper and Ichniowski (257) found methyl cellulose and S-methyl isothiourea effective in combating the action of histamine while the common pressor substances are less effective.

c. *Epinephrine.* Epinephrine and its pharmacologically related agents are by far the best general antagonists of the effects of histamine upon tissues, particularly smooth muscles (258). Epinephrine is a powerful antagonist of the action of histamine on the guinea-pig lung (125). Its use in allergic conditions is too well known to need further discussion. When epinephrine is given to patients with either spontaneous or histamine-induced headaches, relief from pain is prompt (77). Epinephrine counteracts the increased permeability of the endothelial wall, produced by zylene application or injection of staphylococci suspensions into the rabbit skin (259, 260), and interferes with allergic skin tests (261). The effect of epinephrine upon the triple response of the human skin following histamine injection has been described by Barroso (262). When a 1:2000 solution is injected along with histamine (1:4000) there is definite impairment in the development of the wheal. If epinephrine is injected two or three minutes before histamine, wheal formation is almost entirely prevented. Barroso concludes therefrom that histamine acts more quickly than epinephrine on the small vessels of the skin and, if time is

allowed for epinephrine to act, the antagonism against histamine whealing can be easily observed. Hechter (263), however, was unable to find any potentiating effect of removal of the adrenal glands on the action of histamine on permeability of the rabbit skin capillaries.

d. *Xanthines.* The xanthine derivatives relax most smooth muscles other than those of blood vessels. The antihistamine effect of xanthine, theobromine, caffeine, theophylline, and aminophylline, as well as their antianaphylactic effect on sensitized smooth muscles, is reported by Hechter (263) and Young and Gilbert (264). The latter found that aminophylline (75 to 82 per cent of theophylline plus 12.3 to 13.8 per cent of ethylenediamine) is especially effective in counteracting the bronchospastic effect of histamine in guinea pigs.

The xanthines are also effective in relaxing the bronchi of man constricted by histamine or asthma. Greene and coworkers (265) have obtained relief in cases of bronchial asthma following administration of theophylline. These investigators report that a definite increase in vital capacity accompanies the symptomatic relief by the drug, and that asthmatic patients refractory to other drugs frequently respond favorably to theophylline.

Aminophylline, administered intramuscularly, has also proved valuable in the treatment of bronchial asthma, especially in patients refractory to epinephrine (34); oral administration of the drug is usually ineffective. Hermann and Aynesworth (266) have reported favorable results in a series of cases of status asthmaticus in whom the drug was injected intravenously.

Caffeine has been used in combination with analgesics and hypnotics in the treatment of headaches and migraine (34).

e. *Desensitization to histamine by repeated exposure to histamine.* There is much experimental and clinical evidence to indicate that repeated exposure to histamine diminishes the susceptibility of a tissue to the amine. The first attempts to induce desensitization or refractoriness to histamine by injection of increasing doses of the compound were reported by Ramirez and St. George (267) in 1924. Karady and Bentsath

(268) also observed that man becomes resistant to the action of the drug after several weeks following daily subcutaneous injections of the amine. Prolonged pretreatment with histamine in man is said to prevent the development of the flare of the customary triple response following intracutaneous injection of the drug (269). There is no evidence, however, that a diminution in the whealing response of the skin has ever been accomplished by such procedures.

Increased tolerance to histamine has been demonstrated with the cat, guinea pig, rabbit, and dog. S. Karady (270) finds that cats pretreated with repeated daily doses of the amine are protected against the depressor effects of a small intravenous dose of histamine. Essex and Horton (269) also claim that repeated subcutaneous injections of histamine afford some protection in guinea pigs against an intravenous lethal dose of the drug.

Smith (271) reports that graded injections of histamine for two or three weeks not only raise the tolerance of guinea pigs to histamine but furnish considerable protection to anaphylactic shock from horse serum. Similar results have been obtained by Farmer (272) with oral administration.

E. S. Karady (273) concluded that the progressive decrease in the fall of blood pressure with daily injection of the same quantity of histamine in dogs is a manifestation of true tolerance. This type of functional reaction is sharply differentiated from tachyphylaxis, an adaptation to a second injection of histamine shortly after an animal has recovered from a much smaller dose, as observed by Karady and by Eichler and Killian (274). The latter were able to treat rabbits with as much as 150 mg. of histamine without fatal outcome provided this were done within 30 minutes after a preliminary small injection.

Katzenstein (275) reported that tolerance to histamine can be developed in the dog by daily, repeated intravenous injections of carefully graded increasing quantities of the drug. Such tolerant animals have only mild and transitory reactions to amounts of histamine that are followed by severe prostration and even death in the untreated animals.

That desensitization against histamine does not depend on a production of specific neutralizing antibodies is suggested by

the fact that hydrochloric acid secretion of the stomach following histamine stimulation is not affected by prolonged treatment with histamine, as shown by Stroembeck (276) and by Wells, Gray, and Dragstedt (277). A physiologic antagonistic mechanism for repeated injections of histamine is suggested by Adarii (278) and others (279) who believe that histaminase production is increased. There appears to be no direct evidence, however, to support this suggestion.

The mechanism of increased resistance to histamine may also be related to increased activity of the adrenals. Thus MacKay and Clark (280) found that the adrenals of rats that had been given daily subcutaneous doses of histamine weighed 31 per cent more than those of the control. The hypertrophy, however, was confined to the cortex. Essex and Horton were not able to distinguish between the adrenals of the treated animals and their controls, either on a basis of microscopic or gross examination. Nor did Katzenstein (275) find cortical hypertrophy in dogs which developed increased tolerance to the drug. In the light of these findings the suggestion that the adrenal glands play a role in protecting against the effects of a lethal dose of histamine might appear to be weakened. However, the ability of the adrenal glands to influence histamine sensitivity may not necessarily be reflected in terms of the weight of the glands or their histologic appearance. The work of Selye (281), MacKay and Clark, and others (145–154) on the role of the adrenal glands of the rat in the development of resistance to histamine cannot be dismissed without giving consideration to the possibility that the adrenal secretions may be important in the development of such resistance.

Edholm (282) has shown that prolonged treatment of cats with histidine diminishes the sensitivity of this animal species to effects of the drug. One explanation for this finding might be the fact that histidine as a rule contains traces of histamine. Consequently, the increased resistance against histamine after chronic histidine administration might be due to a chronic administration of traces of the drug itself.

f. *Antibodies to histamine induced by histamine conjugates.* Interesting results have been reported by Fell *et al.* (279, 283,

284) and by Cohen and Friedman (285, 286, 287) on the inhibition of the histamine effects by previously treating sensitized animals and allergic individuals with a complex antigen of the amine and a protein (globulin of horse serum). Landsteiner (288) had shown some years ago that when simple chemicals are diazotized and coupled with a protein, an antigen is formed. The specificity of the resulting antigenic complex is determined by the hapten portion. Histamine itself is nonantigenic; it becomes antigenic when conjugated with some substance possessing antigenic properties. Histamine azoproteins were successfully prepared by Fell *et al.* (279, 283) by binding histamine to an intermediary aryl amine which is diazotized and coupled to despeciated horse globulin. Immunological studies, carried out in rabbits, guinea pigs, and man, indicate that a precipitin is induced by the histamine azo horse protein which is specific for the histamine (hapten) end of the compound. Animals immunized with this antigen acquire a marked ability to detoxify the drug, and a definite increased resistance to anaphylactic shock and to the histamine locally released after combination of the antigen with the antibody in sensitized rabbits. Sheldon, Fell, and their co-workers (279) report that they used the antigen with some success in clinical allergy. Cohen and Friedman repeated these studies and reported that they could produce antibodies against histamine in human beings by injection of the compound and that certain treated persons developed the capacity to neutralize histamine in vitro (286) and in vivo (287). These observers believe that some protection is given allergic individuals by such treatment. Quite similar results on rabbits and guinea pigs with a synthetic antigen prepared by coupling the isocyanate derivative of histamine with despeciated serum globulin are also described by Rodney and Fell (284). Whether any of these substances offer real protection against significant increases in histamine or in allergic diseases remains to be seen. While the reported results appear promising, confirmatory findings have not been published.

g. *Benadryl.* Recent studies in the laboratories of Parke, Davis and Company by Loew et al. (289), (290) show that

synthetic benzhydryl alkamine ethers are capable of preventing fatal histamine and anaphylactic shock in guinea pigs. In alleviating bronchoconstriction induced in these animals by administration of histamine intravenously or by inhalation of atomized aqueous solution, the potency of several of these compounds (beta-dimethyl-aminoethyl, and beta morpholinoethyl benzhydryl ether) are said to be two to four times greater than that exhibited by the Fourneau histamine antagonists 929 F and 1571 F. The acute toxicity of beta morphylinoethyl benzhydryl ether is approximately one-half that of beta dimethylaminoethyl benzhydryl ether but because of the high potency of the latter compound its therapeutic index is greater (289). The antianaphylactic activity of these two compounds indicates that they are probably the most potent compounds studied so far.

The hydrochloride of beta dimethylaminoethyl benzhydryl ether, known as benadryl, has been extensively studied by various groups at the Mayo Clinic and reported on in November of 1945. The drug is a white crystalline powder which is soluble in water and alcohol and is stable under ordinary conditions of temperature and pressure.

McElin and Horton (291) report that benadryl is fifteen to thirty times more active than aminophylline in counteracting bronchial constriction caused by histamine shock in guinea pigs, 650 times more active than papaverine in antagonizing histamine on isolated muscles of the guinea pig ileum. Compared further with papaverine, it is found to be fifty times as effective in antogonizing acetylchloine, and 1.3 times as effective in antagonizing the contractile effects of barium chloride. The antispasmodic activity of the drug is thus claimed to have three components: 1) an antihistamine action; 2) an antispasmodic action (antibarium chloride effect); and 3) an atropine-like effect (anti-acetylcholine action).

McElin and Horton also made toxicologic studies on mice, rats, rabbits, and dogs. Massive doses produced violent excitement, convulsions, respiratory failure and death. Nonlethal toxic doses produced excitement and violent ataxia in dogs. When large nontoxic doses were given to dogs over a long period, there were no changes in the red and white cell counts

of the blood, or differential white count, or in the hemoglobin or blood nonprotein nitrogen levels. No evidence was found of acute or chronic degeneration of any of the tissues. However, a curious and unexplained marked congestion of the choroid plexus occurred.

The clinical studies of benadryl as carried out by the Mayo group are extremely encouraging. McElin and Horton report that beneficial results were obtained by the oral, intramuscular and intravenous routes in 1) decreasing the cutaneous vasodilating action of histamine, 2) alleviating nasal congestion induced in the mucous membrane by histamine, 3) decreasing the acidity and volume of gastric secretion produced by histamine, and 4) depressing the flare and wheal responses in cases of hypersensitivity to cold.

The only clinical report so far available on the use of benadryl besides that of the Mayo group, to be reported here in some detail, is that of Curtis and Owens (292), of Ann Arbor, who published in April of 1945. They administered benadryl to a group of eighteen patients with acute and chronic urticaria and noted prompt relief of symptoms in eleven of their patients, definite improvement in three and no benefit in four. O'Leary and Farber (293) also report that benadryl is highly effective in the treatment of urticaria and angioneurotic edema. Of fifty patients who received the drug for urticaria, thirty-four were completely relieved, twelve were definitely improved, four experienced no benefit. In a majority of cases of the Mayo group, relief was obtained only while the drug was being used. The drug is, therefore, palliative and not curative, although in some instances it seemed to break the urticarial cycle.

McElin and Horton (291) employed benadryl in hay fever and vasomotor rhinitis and report remarkable results. The dose by mouth ranged from 50 to 500 mg. per day, that by intramuscular injection was 20 mg. per injection. In some instances 10–120 mg. was given intravenously within a ten-minute period by the continuous drip method. In the majority of patients obtaining relief from benadryl, continued use of the drug was found necessary in order to keep them symptom free.

The drug was not found effective in a few cases of established Meniere's disease, histaminic caphalgia, migraine, atypical face and head pains, contact dermatitis. It was found effective, however, in early Meniere's disease, urticaria, angioneurotic edema, and tension headache with vasodilating features.

The chief side effects observed in one hundred patients were sleepiness, dizziness, dry mouth and a feeling of nervousness. None of the reactions appeared to be sufficiently marked to warrant discontinuation of the drug.

Koelsche, Prickman, and Carryer (294) also reported on a series of eighty-three patients with hay fever, bronchial asthma, or the two in association. The undesirable side effects were much more apparent in their series of patients than in those of McElin and Horton. The dosage employed was 50 to 100 mg. by mouth, three times daily. Out of fifty-two patients with hay fever only, thirty-nine, or 75 per cent, reported benefit, while thirteen, or 25 per cent, reported no help. Of the thirty-nine who reported beneficial results, ten obtained almost complete relief, nineteen claimed 75 per cent relief, and ten reported at least 50 per cent relief. Of the thirteen not relieved, eight stopped the drug because of unpleasant side effects; five took the drug long enough to give it a fair trial.

Their observations on nineteen patients afflicted with hay fever associated with asthma gave about the same results; fourteen, or 74 per cent, were benefited, five were not. Of the fourteen who received benefit, five noticed improvement of the hay fever but not of the associated asthma.

The results of Koelsche and associates with benadryl in patients afflicted with bronchial asthma alone are less encouraging. Of twelve patients treated, four reported benefit, while eight reported no improvement. As regards the use of the drug in asthma, the authors state that considerably more experience is needed before definite conclusions of its usefulness and its limitations can be drawn.

Williams (295) has also reported encouraging results with benadryl in a limited number of cases of perennial vasomotor rhinitis and hyperplastic ethmoiditis. Ten of twelve patients having perennial vasomotor rhinitis obtained 90 per cent relief; two obtained no relief. These two patients experienced

such extreme dizziness after taking 50 mg. of the drug that they were unwilling to continue treatment. The effect of benadryl in perennial vasomotor rhinitis appears to be superior to that of niacin. Of four patients with hyperplastic ethmoiditis, all received marked symptomatic relief with retraction and disappearance of polypoid tissue and diminution or disappearance of purulent discharge. In all cases, however, symptoms tended to return within twelve hours after cessation of the drug.

Williams estimates that in two cases of Miniere's disease 75 to 80 per cent relief of symptoms was obtained with benadryl. When treatment with a combination of niacin and potassium nitrate was carried out, however, both patients felt that the relief was much greater. Furthermore, in one case the associated vasodilating type of headache which tended to occur in the intervals between the attacks of vertigo was relieved by niacin plus potassium nitrate but not by benadryl.

In myalgia of the head, only moderate (40 to 50 per cent) relief was obtained in five patients with the drug. All five patients reported that the relief obtainable from niacin was definitely greater than that obtainable from benadryl.

Logan (296) reported on the use of benadryl in the treatment of eighteen children suffering from several of the allergic diseases. In nine of twelve cases of hay fever excellent or good results were obtained. Three patients of this group had associated asthma. The results of treatment for these were recorded as good in one case, fair in another and questionable in the third. Good results were also obtained in a few children with vasomotor rhinitis and urticaria.

It is suggested that 2 mg. per pound of body weight is an effective dose in most instances for children.

The combined results of the various groups reported indicate that benadryl is extremely useful in 1) acute and chronic urticaria, 2) hay fever, and 3) perennial vasomotor rhinitis. It is of some value in 1) Meniere's disease, 2) bronchial asthma, 3) histaminic cephalgia, 4) tension headache with vasodilating features, and 5) myalgia of the head. In general the toxicity to benadryl is low and there appears to be a wide range between the therapeutic and serious toxic effects of the drug (297). In

some instances, however, disagreeable responses to the drug definitely diminished its clinical usefulness.

h. *On the possible mode of action of certain antihistamine substances.* A number of drugs reduce or counteract the reaction of tissues to histamine by directly opposing histamine action in consequence of their own biologic activity. The most commonly employed antispasmodics to smooth muscle are epinephrine and other sympathomimetic amines, papaverine and its relatives, theophylline and its relatives, and to a lesser extent the nitrates and related compounds; atropine is also included in this grouping by some writers (297, 298). The mode of action of several of these drugs has been discussed already; some are valuable in certain conditions, but the value of all is limited.

Although atropine is best known for its inhibitory effects on vagal and other parasympathetic nerve endings (cholinergic nervous system), it does have antihistamine properties. These were clearly shown in the original report by Dale and Laidlaw (59). In sufficient quantities, atropine will reduce or eliminate the response of smooth muscle preparations to small quantities of histamine. Likewise, in ample doses it will reduce the secretory response of the salivary, pancreatic and gastric glands to histamine (59, 299). Usually, however, the doses of atropine necessary to produce antihistamine effects exceed those capable of reducing the effectiveness of cholinergic activity. Likewise cholinergic reactions are apt to be more affected by a given dose of atropine than are the histamine responses (297). Atropine, therefore, belongs more definitely to the anticholine than to the antihistamine group of compounds.

Dragstedt (298) has pointed out that none of the commonly employed drugs oppose all of the actions of histamine and most of them have other actions which have to be taken into consideration. Atropine, for example, is quite effective against the secretory stimulation of histamine to the pancreas, less so against the secretory stimulation to the stomach, but without much effect against the vascular and smooth muscle action of histamine. Some agents, urogastrone for example, appear to

be more effective in inhibiting the histamine response of gastric secretion than of other secretions (300). Epinephrine, on the other hand, is fairly effective against the smooth muscle action of histamine, but almost ineffective against its secretory action. Its action as a histamine antagonist was studied in detail by Dale and Richards (299). Theophylline and papavarine are fairly effective against the smooth muscle action of histamine but do not oppose its vascular or secretory effects (297).

Certain other antihistamine drugs produce their effects by specific properties. Such is the case of the amino acids histidine, arginine, and cysteine, etc. The imine =NH radical of these amino acids is visualized as competing with a like =NH group of the imidazol ring of histamine for attachment with chemical receptors of smooth muscle. An excess in the tissues of any amino acids possessing such a radical saturates the chemical receptors of the tissues; thus histamine cannot combine with the receptors and produce its characteristic effects (246). These compounds do not have promise as therapeutic agents for enormous quantities are required to antagonize even small amounts of histamine.

Because attention is certain to be focused on antihistamine drugs in the future, an examination of the actions of benadryl even at this early date seems justifiable. McElin and Horton (291) have indicated that the antispasmotic action of the drug has three components, an antihistamine action, an antispasmodic action and an atropine-like effect. The exact site at which it produces its effects needs further study. Its similarity to other antihistamine agents is still not known. While the effect of benadryl in the skin as noted by McElin and Horton (291) and as indicated by its action in the series of patients with urticaria (291, 292, 293, 296) might be related to an altered reactivity of the skin to histamine (233), the drug may affect the skin directly through blood vessels or indirectly through nerves (57). Whether the disappearance of the wheals and the relief of pruritis in urticaria, or the shrinkage of the mucous membrane in hay fever, is due primarily to its influence on blood vessels or on nerves has not been demonstrated. It should be pointed out that a number of antihistamine drugs have an anaesthetic effect on pain nerve

endings in the skin (254, 256, 301). Logan (296) has indicated that if an elixir of benadryl is held in the mouth for a short time, anaesthesia of the tongue occurs.

The suppression of mucous secretion in hay fever patients and the production of dryness of the mouth in most subjects taking the drug indicates that benadryl has an antisecretagogue action. This might be due to direct blockage of the secretagogue action of histamine (297). Suppression of such secretions might, on the other hand, be interrupted as an atropine-like effect. The action of benadryl on gastric secretion induced by histamine as indicated by McElin and Horton (291) is not clear. Code (297) mentions that other antihistamine drugs have not had much effect on gastric secretion stimulated by histamine whereas they have reduced normal secretion and he suggests that the failure of benadryl to be effective in many cases of asthma may be a parallel situation.

Code very wisely warns that although the effects of this and other related drugs are certainly associated with histamine, they may not be exclusively so. The fact that a drug relieves symptoms of allergic diseases, which can for the most part be duplicated by injected histamine, is not conclusive proof that such symptoms are due to histamine. He nevertheless states: "For the present it is clear, however, that benadryl and similar compounds are drawing together a widely diversified group of clinical conditions whose common denominator seems likely to be some abnormality of histamine metabolism."

Of the possible methods of avoiding, reducing, tolerating or counteracting histamine and allergic reactions, it is premature to predict which will have the greatest value. Continued search for antihistamine drugs is most important. Such drugs should be helpful in elucidating many unsolved physiological problems, and their clinical usefulness can hardly be overstated. Already benadryl gives great promise as a therapeutic agent. It certainly points the way to other chemical agents of greater clinical value. That there will be more potent and less toxic antihistamine compounds than those now available seems certain.

5. Therapeutic Use of Histaminase and Histamine

A. *Histaminase.* The enzyme histaminase (diamine oxidase) is regarded as an inactivator of histamine under appropriate conditions and presumably does so as a normal physiological process. The possibilities of histaminase inactivating lethal doses of histamine in animals have already been recited (page 165). There is also evidence to indicate that the enzyme, when given to sensitive animals prior to the shocking dose, diminishes or prevents anaphylaxis, and when given to allergic individuals prevents, ameliorates, nullifies, allergic reactions. Karady and Browne (136), 1939, Barlow and Homburger (302), 1941, Frank and Harris (303), 1941, report that oral or parenterally administered histaminase materially influences both the course and fatal effects of otherwise lethal doses of intravenously administered antigen in guinea pigs.

Based on the assumption that histamine is a causative factor in allergic reactions, methods of potential control and management have been suggested and tried in which large amounts of the enzyme are given orally or parenterally. The use of histaminase in allergic and other conditions has now led to a large literature. For the sake of brevity little reference will be given to individual work. It is interesting to note that some of the suggested methods of treatment were established in clinical practice before any substantial implication had been demonstrated (304).

Among the clinical conditions in which this enzyme is said to be of value are serum sickness, food allergy, unilateral headache, acute and chronic urticaria, allergic rhinitis, asthma, Meniere's syndrome, anaphylactic reactions, dermatitis and peptic ulcer. Those who support the claims of beneficial effects from the use of histaminase are: Ercklentz and Ercklentz (305), 1936, in gastritis, peptic ulcer, hepatic cirrhosis and colitis; Abel, Siebert, and Earp (306), 1936, in contact dermatitis and serum sickness; Adelsberger (309), 1937, in allergic rhinitis; Roth and Rynearson (310), 1939, in allergic reactions to insulin; Foshay and Hagebusch (311), 1939, in serum sickness; Ertl (312), 1939, in hay fever and eczema; Layman and Cummings (313), 1939, and Layman (314), 1940, and Goldberg (315), 1940, in chronic urticaria; Altose

(316), 1940, in urticaria and angioneurotic edema; Baker (317), 1940, in cold allergy; Forman (318), 1940, in urticaria, angioneurotic edema, acute coryza, asthma, contact dermatitis; Roth and Horton (319), 1940, in serum sickness, urticaria, vasomotor rhinitis, erythromelalgia of the head; Eustis (320), 1940, in asthma; Cherry and Prickman (321), 1941, in serum sickness; Taylor and Hilger (322), 1941, in allergic reactions to liver extract; O'Hallaren (323), 1941, and McHardy and Browne (225), 1944, in peptic ulcer, and Horton (224), 1943, in histamine cephalgia. The latter worker has stated: "That histaminase can be used as a therapeutic agent when taken by mouth is, in my experience at least, definitely established."

On the other hand, equivocal and unfavorable results have been obtained by many, including Kile and Rusk (324), 1940, in cold allergy; Keeney (325), 1940, in hay fever; Miller and Piness (326), 1940, in various allergic conditions; Alexander (327), 1940, in asthma and hay fever; Knoll and Beinhauer (328), 1940, in acute, chronic and physical urticaria, asthma, hay fever, serum sickness, allergic gastro enteritis, and allergic rhinitis; Sulzberger (329), 1940, Guy (330), 1940, Brunsting (331), 1940, in a variety of allergic conditions; Frank and Harris (303), 1941, in asthma, vasomotor rhinitis and urticaria; Vaisberg (332), 1942, in vasomotor rhinitis, dermatographia, migraine, and chronic urticaria; Peshkin *et al.* (333), 1943, in hay fever, asthma urticaria, and cold allergy; Frank (334), 1943, in hay fever; Ratner (104), 1943, in various allergic states. Experimental studies by Maisel and Abramson (335), 1940, Simon (336), 1940, Miller, Hawes, and Piness (337), 1941, demonstrated that histaminase had no effect on wheal formation and other phases of allergy. Likewise Knoll and Beinhauer (328), found that intracutaneous wheals produced by histamine in normal and allergic persons are not altered by oral pretreatment with histaminase. Rose (103), 1941 observed the symptoms and histamine content of the blood of 36 allergic patients in the course of the administration of histaminase, both oral and intramuscular. No effect was noted on the histamine content of the blood following or during the administration of histaminase. Slutzky *et al.* (338),

1942, found histaminase of no value in the treatment or prevention of peptic ulcer in dogs.

While one may argue that the evidence in favor of the use of histaminase in allergy is as convincing as that which does not support it, the general impression is gained that histaminase therapy has already gone into discredit. The reviewer has found only three or four references in the literature during the past two years which report favorable results with histaminase.

It is difficult to account for the divergent clinical results with the enzyme. In some instances, of course, improvement may have been influenced by a natural tendency, based on wishful thinking, to see favorable results. Experimental results with animals have not been unequivocal either. The findings of Karady and Browne (136), Barlow and Homburg (302), and Frank and Harris (303) with respect to the prevention of anaphylaxis in guinea pigs were not sustained by Alexander and Bottom (137), 1940, Corper and Cohen (339), 1940, Neeley (340), 1941, Hawes, Alles, and Miller (341), Knoll and Beinhauer (328), 1941, Younger *et al.* (138), 1941, Ratner (104), 1943, and others. Necheles and Olson (342), 1941, report that histaminase has no depressant effect on the salivary, gastric, biliary, and pancreatic secretion of dogs stimulated by histamine or on gastric secretion following a meat meal. The investigations of Ratner (104) over a period of ten years have failed to show that intravenous or intramuscular administration of histaminase has any effect on histamine present in the body or on that given by injection. Complete failure to reduce the histamine content of the tissues by histaminase is also reported by Dragstedt (139).

The fact that the enzyme cannot completely protect experimental animals against highly toxic doses of histamine or against anaphylaxis does not indicate that histamine would have no value in alleviating symptoms of allergy. The liberation of histamine in the latter is presumably gradual and less explosive than in experimental anaphylaxis. The rate of inactivation under such conditions might be sufficient to have antidotal value. And, of course, only relatively impure preparations have so far been used.

It is difficult, however, to suppose that histaminase given orally would inactivate histamine in the intestine, as suggested by Eustis (320), and thus prevent the absorption of the toxic amine. It is most unlikely that such would occur since the enzyme is itself rapidly destroyed by the digestive ferments. Oral administration does not increase the histaminase activity of the blood (139).

Vaisberg (332) suggests that the beneficial effects of histamine observed by various authors are due to something else in the preparation other than the enzyme-system histaminase. He, along with many others, believes that the very properties of the enzyme militate against its ability to relieve the ill effects of released histamine in anaphylactic shock and allergic reactions. The destruction of histamine in the body is not instantaneous and is generally quite slow. The likelihood of an appreciable increase in histamine in the body being counteracted by the enzyme before its toxic effects have been produced seems remote to Vaisberg who maintains that any beneficial action which histaminase might have by oral administration is due to something else in the protein of the hog kidney or intestinal mucosa, from which the enzyme is usually prepared.

Most workers will probably agree with Best and McHenry (343) that there is little or no physiologic basis on which to rest its clinical use. Very active enzyme preparations might possibly have a demonstrable effect. While some workers believe that histaminase as a tool for combating excessive histamine liberation must be postponed until less toxic and more potent histaminase preparations can be secured, others maintain that there is no particular reason to believe that the pure enzyme would be any more effective.

B. *Histamine.* While the therapeutic value of histamine is generally regarded as unimportant, its use in recent years has definitely increased. The drug might be a more effective agent were its actions selective and its side actions less marked. The latter are so pronounced that they often preclude the possibility of certain clinical applications. The chief therapeutic

value of histamine has been in connection with desensitization or hyposensitization to liberated histamine and in the treatment of arthritis and peripheral vascular disease by iontophoresis.

a) *Desensitizing effect of histamine on histamine action and on anaphylaxis.* Various authors have shown that it is possible to induce refractoriness to histamine in animals and in humans by repeated exposure to the drug. Fuehner (344), apparently, was the first to show such refractoriness to histamine in rabbits. This was confirmed by Oeheme (345) and many others (267–275). (See p. 188.) Refractoriness in man was first observed by Lewis and Grant (346).

Nonspecific desensitization of sensitized animals with prevention of anaphylactic shock was first reported by Karady and Bentsath (247) in guinea pigs. Using the Schultz-Dale technique, Farmer (272) showed that uterine strips of serum sensitized guinea pigs treated with histamine are less sensitive to the assaulting antigen than untreated controls; oral administration is also said to induce partial refractoriness. The most convincing and direct evidence indicating that pretreatment with histamine protects guinea pigs against fatal anaphylaxis is presented by E. S. Karady (273). Similar results are reported by Miyamoto (348), Frank and Harris (303), Smith (271).

While there is reason to believe that the organism can become more resistant to repeated injections of the drug, the manner in which it does so is still unknown. Reference has already been made to the possibility of the adrenal cortex having a role in the diminished responsiveness of the tissues to further encounters with the amine (page 190). Since histamine discharges epinephrine from the adrenal glands (Szczygielski (349), Feldberg (113)), this might further explain how repeatedly injected histamine brings about a non-specific tolerance or mithridatization. A rapidly developing refractoriness or tachyphylaxis to the blood pressure effects of histamine has been claimed by certain authors (270, 274, 275). However, other extensive investigations have failed to confirm these findings (350, 351). Wells *et al.* (277) have pointed out that tachyphylaxis to histamine, as indicated by the gastric

secretory response in dogs, does not occur when the drug is administered subcutaneously to animals with total gastric pouches. These workers express the opinion that animal experiments have failed to provide an experimental analogy for the therapeutic effect claimed by histamine desensitization in allergy. Then, too, antianaphylaxis does not occur in animals; i.e., animals will react over and over again in a predictable manner with no diminution in sensitivity, as has been shown by Neely (340), Manteufel and Preuner (352), Kallos and Pagel (353), and Ratner (354). Furthermore, the persistence of allergic reactions in patients for many years without spontaneous subsidence would argue that such a tolerance is not easily achieved.

This diminished responsiveness of tissues to histamine and anaphylaxis constitutes the basis for the non-specific desensitizing treatment of allergic disease, which consists of the injection of small but gradually increasing doses of histamine. According to some observers, particularly Farmer (192), the possibility of achieving refractoriness to histamine reduces the treatment of allergic diseases to a common denominator and thereby makes for simplification. Furthermore, it is claimed to be useful in all cases of multiple sensitiveness in which several allergens have to be used for specific desensitization and also in those cases in which the causative allergen or allergens cannot be discovered.

b) *Commoner allergic conditions.* Although the rationale of desensitization treatment has not been adequately explained, the results reported by various workers seem to be satisfactory in some instances. The first reference of the use of histamine in allergic conditions was reported by Ramirez and St. George (267) in 1924 for asthma. Since then, histamine has been reported valuable in the treatment of migraine by Friedlaender and Petow (355); in urticaria by Ernestine and Banks (356), Gajdos (357), Dzsinich and Paul (358), Joltrain (359), and Alexander and Elliott (360); in insulin sensitivity by Collens and his associates (361); in cold allergy by Horton, Brown, and Roth (205), Horton and Brown (206), Bray (362), Roth and Horton (307), Horton and Gabrielson (363); in bronchial

asthma by Stahl and Masson (364), Piquet (365), Thiberge (366), Dzsinch (367), Farmer (124), (192); in vasomotor rhinitis and hay fever by Dzsinich (367), Farmer (124), (192), Farmer and Kaufman (368), Barroso (369), Thiberger (366), and Gant *et al.* (370).

Farmer (124, 192) has used histamine phosphate in the treatment of asthma, vasomotor rhinitis and hay fever for more than six years at the Lenox Hill Hospital. It is his opinion that the amount of drug given by the older workers (30 to 750 gammas per injection) is much too high. Acting on Dzsinich's suggestion to use small initial doses, Farmer employs .1 gamma subcutaneously in milder cases of asthma and .01 gamma in severe cases. In preseasonal treatment to hay fever the initial dose is 0.1 to 1.0 gamma; in children .01 gamma. The injections are increased each time by 50 per cent, if well tolerated, and in the beginning they are given two to three times weekly. They are later spaced at five to seven-day intervals. In asthma and vasomotor rhinitis the maximum dose in adults is 50 to 75 gamma, in hay fever 100 to 200 gamma. The increase in dosage, the spacing of the injections and the number of injections given are dependent upon the patient's tolerance, age, and on the results achieved. The precautions to be taken are said to be the same as in specific desensitization. Farmer believes that histamine treatment causes less severe and less frequent systemic reactions than specific desensitization. In the course of several thousand injections of histamine he claims to have encountered systemic reactions in a few instances only. His detailed observations in 54 patients suffering from asthma and vasomotor rhinitis are reported to be encouraging and warrant continued investigation (192).

As regards the over-all results of this method of management of allergic conditions, even the most optimistic appraisal leaves much to be desired.

c) *Histamine by mouth in the treatment of vasomotor rhinitis.* Gant and his associates (370) at the Allergy Clinic of the Massachusetts General Hospital have studied the effect of oral administration of histamine in a large number of cases

of vasomotor rhinitis in which other methods of treatment were unsuccessful. Contrary to most statements, histamine is absorbed from the gastrointestinal tract and produces the same physiologic reactions as does the parenteral injection. Their method is to start with one drop of a 1:1000 dilution in a glass of water, on an empty stomach, and to note the reaction. Too large a dose aggravates the symptoms, too small a dose causes no change; the correct dose relieves the patient within fifteen to twenty minutes. If no bad effects are observed, the patient is advised to increase the dosage one drop each day until toxic effects appear. Thereafter, he receives a maintenance dose, just below the toxic level, which is repeated when necessary to control the symptoms. Dosage may vary from one drop of 1:1000 dilution to twenty-five drops of 1:1000 dilution, the average being five to seven drops of the 1:1000 dilution. The object of the treatment is not to build up a general resistance to histamine, but rather to control the symptoms by repeated small doses. Symptomatic relief is usually prompt. With recurrence of symptoms, another dose is taken; the histamine is needed less frequently as time goes on. The occurrence of good results in all except a few cases would indicate the results are more than a coincidence. The dosage being delicate and the variabilities in absorption great, the authors stress the necessity of observing rigidly basic conditions. The method is not claimed to be a panacea; it is claimed, however, to bring results superior to other methods for symptomatic relief of vasomotor rhinitis.

These results contradict somewhat the current attempts to explain the effect of histamine in allergic diseases on the basis of mithridatization of histamine.

d) *Immunity against histamine by histamine azoproteins.* The clinical studies of Shelton, Fell, and associates (283, 284) and of Cohen and Friedman (285–287) should be mentioned again here. It will be recalled that these workers claim to have developed marked tolerance to histamine in patients by repeated administration of histamine azoproteins; this is said to produce an immunity against the histamine (hapten) portion of the antigen. Hay fever patients so treated are reported to be benefited. Confirmatory findings are being awaited.

e) *Histamine cephalgia.* Horton and associates (77), (240) maintain that histaminic cephalgia, associated with its clinical and laboratory evidence of vasodilation, is unique in its symptomatology and its response to histamine therapy. Attacks can be induced at will with given amounts of histamine and can be eradicated by desensitization with histamine. Horton (77) states: "The spectacular manner in which patients respond indicates that histamine treatment is as specific for this syndrome as insulin is in the treatment of diabetes mellitus." The statement is undoubtedly questioned by many. Nevertheless, the efficiency of histamine hyposensitization therapy in histamine cephalgia is confirmed by Lieder (371) and by McHardy and Browne (225). The possibility that the injection of histamine may influence favorably the symptoms of post-traumatic headache is suggested by results of Friedman and Brenner (209).

f) *In Meniere's disease.* Shelton and Horton (372) and Horton (373, 374) report that the intravenous administration of histamine (2.75 mg. of histamine diphosphate in 250 cc. of isotonic solution of NaCl administered at the rate of 2 to 5.5 cc. per minute, depending on the tolerance of the patient) is an efficient form of therapy in Meniere's disease. Horton claims that it aborts the acute symptoms of this complex in the majority of instances. It is not necessary to hospitalize patients for this procedure. Atkinson (216), McHardy and Browne (225) also endorse the procedure of "histamine desensitization" in Meniere's Syndrome.

Lillie, Horton, and Thornell (375) report improvement in deafness in 12 of 25 cases of Meniere's symptom complex following intravenous injections of histamine. Improvement in tinnitus in 14 cases and in vertigo in 21 cases following treatment is also claimed. The authors state that the method of giving histamine intravenously in 1:250,000 dilution is a simple procedure. Several thousand injections of this type have been given to patients with Meniere's symptom complex at the Mayo Clinic without producing any unfavorable results.

Peters and Horton (376) have recently (1945) reported that histamine in .8 per cent KCl is more effective in relieving pain

than histamine in .8 per cent NaCl. They state, however, that the vertigo and tinnitus of Meniere's disease are improved whether the histamine is given in a solution of KCl or NaCl.

g) *Treatment of multiple scleroses by the intravenous administration of histamine.* Horton *et al.* (377) report that 18 out of 24 patients with acute multiple sclerosis improved under daily intravenous administration of 2.75 mg. of histamine diphosphate in 250 cc. of .9 per cent NaCl, given at the rate of 2–6 cc. per minute depending on the tolerance of the patient. The average patient received forty to fifty such injections; the minimal number was thirteen and the maximal number was three hundred. The prompt improvement that follows histamine therapy is said to result from vasodilation in the central nervous system.

Of 78 patients who had an advanced or chronic form of the disease, 36 showed varying degrees of improvement, ranging from 10 to 95 per cent. The remaining 42 patients showed no objective improvement, although many were stated to be subjectively improved. The authors state that with ocular manifestations, such as the loss of vision and paralysis of the ocular muscles, recovery seems to be more rapid and complete with histamine therapy than with other forms of therapy.

h) *Miscellaneous.* Horton (224) makes the interesting but puzzling statement that in 10 cases of histaminic cephalgia in which ulcers resulted secondarily from attacks of cephalgia, treatment of the latter by means of histamine desensitization, and without other treatment for the duodenal ulcer itself, not only eradicated the attacks of histaminic cephalgia but permitted the duodenal ulcer to heal promptly in a period of several weeks. Stimulated by Horton's publication, McHardy and Browne (225) tried histamine desensitization on a group of duodenal ulcer cases sensitive to histamine but not histaminic cephalgia; a distressing accentuation of ulcer symptoms resulted. They conclude that the indications for histamine desensitization should be sufficiently specific to outweigh the possible production of a disease entity so severe as duodenal ulcer.

i) *Histamine ion transfer (Iontophoresis).* The administration of histamine by ion transfer has been advocated by many workers for the treatment of various forms of arthritis and peripheral vascular disease (378–388). Deutsch (378) was one of the first to utilize the procedure of iontophoresis in connection with this drug. He had employed other methods of administration but finally concluded that iontophoresis is the most satisfactory. Kling (389) studied the relative efficiency of histamine as compared with mecholyl (acetyl-beta-methylcholine) and doryl (carbaminoylcholine chloride) by means of the triple-response method. He reported that a 1:1000 solution of histamine gives a far stronger wheal and flare than the same concentration of either of the other two substances. By cataphoresis, the maximal response to histamine is reached within 5 to 10 minutes. At this time the increase in temperature of the skin is more marked than that induced by mecholyl, however, the latter appears to be effective for a slightly longer duration; carbaminoylcholine chloride was reported to be unsatisfactory since definite systemic reactions generally follow. The results are interpreted as indicating that histamine is the drug of choice for the production of local vasodilatation without serious systemic reactions.

In the administration of histamine by ion transfer, the most commonly used salt is histamine dihydrochloride. This hydrolyzes in an aqueous solution or unction into positive ions of histamine and hydrogen and negative ions of chlorine. The histamine, being positively charged, is caused to move from the positive pole to the negative pole through the intervening electrolyte, comprising the body fluids, under the influence of a constant potential.

When administered by iontophoresis, histamine first causes a local reaction and then, as more and more is absorbed into the blood stream, systemic reactions (388). The rate of administration can, of course, be controlled by the current flow. The local vasodilatation remains for from one to four hours and constitutes the main local action of histamine. With it comes an increase in blood to the area and a resultant increase in temperature, ranging from 1 to 4 degrees F. These local effects can be made to predominate when the administration is slow,

that is, when the current is low (of the order of 5 milliamperes). When the administration rate is above 0.02 mg. per minute, which is usually above 5 milliamperes, sufficient histamine is absorbed into the blood stream to cause a fall of blood pressure and a feeling of generalized flushing and heat (388).

The circulatory effects of histamine by iontophoresis have been investigated by Abramson *et al.* (390) and by Ets (391). Deutsch (378) reports that histamine by iontophoresis is efficacious in soft tissue involvements, such as bursitis and fibrosis. Patients with polyarthritis are benefited but improvement is not lasting. This is also the opinion of others (386–388), although Kling (379, 380) reported excellent results in arthritis. Vincart-van Geen (381) thought it advisable to use histamine therapy in all acute and chronic cases of periarthritis, in rheumatism, and in cellulitis, but he considers the treatment contraindicated during the initial state of acute infectious rheumatism. Kling and Sashin (382) also tried histamine by iontophoresis in a large group of Raynaud's disease, acroparesthesia, and thromboangitis obliterans; they report that relief of pain occurred in 60 per cent of the cases. Reilly and Knapp (387) also state that histamine iontophoresis is valuable in certain types of specified muscle conditions (as gout, myalgias, strain, and sprain) and in acroparaesthesia and Raynaud's disease; the procedure is not held as a "cure" but a valuable adjunct to the therapy of arthritis.

Hummon (388) has recently reported on his wide experience at Cook County Hospital, Chicago, where some 10,000 histamine treatments were given to over 1,000 patients during the past five years. He indicated the following distribution of patients treated by histamine ion transfer: 40 per cent had post-traumatic conditions, such as those following fracture or dislocation with immobilization; 20 per cent had acute traumatic conditions, such as bursitis, fibrositis, myositis, neuritis, and sprains; 20 per cent had arthritis; 5 per cent had peripheral vascular diseases, and 5 per cent had miscellaneous conditions. Results on patients with acute and post-traumatic conditions were reported good, those with the arthritides were disappointing in that the improvement was not lasting. Results in the

peripheral vascular diseases were not spectacular, but improvement was usually noted after prolonged therapy.

Hummon makes the statement that in all his experience with histamine ion transfer only 8 unfavorable reactions were observed, none of which was severe. The only contraindication is asthma. Patients with hay fever are treated but low current densities are employed.

In view of the favorable clinical reports, it would seem that histamine by iontophoresis warrants further trial.

Thus histamine, a widely distributed constituent of human tissues and a drug of many actions, has provided a basis for innumerable theories of physiological function. While the relationship between its pharmacological action and its physiological role in the human body still remains obscure in many instances, there is growing conviction that its participation in normal and disturbed physiological processes is far more significant than most workers have heretofore realized. Its reported value as a therapeutic agent appears to be well-established in some instances. Certainly, the statement that histamine is a drug of considerable academic interest but little therapeutic importance is subject to revision.

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HEALTH PROBLEMS OF THE AMAZON VALLEY*

J. Allen Scott

In discussing the health problems of the Amazon Valley, let me forestall any disappointment by making it clear at the beginning that I shall only outline the problems, not their solutions. No one really knows the solutions, but efforts are being made to find them. After all that has been published on this region, there is little new to be said, but it may be of value to bring some of the scattered facts into focus as they relate to the problems of public health.

My visit to the Amazon Valley ended about a year ago and was only of two months duration. I have lived for many years in foreign countries and am very conscious of the defiencies of the 90-day wonder who arrives in a strange country speaking the language imperfectly, if at all, buzzes around in areas where travel is easy for three months, asking questions and swallowing whatever answers are given him, and then goes into hiding while he completes his exposition on the country. I well remember and heartily concur in the advice given me by one of the older residents when I first arrived in Egypt many years ago, "Write your book," he said, "before you have been here a year, for after that you will begin to realize how little you know about the country, and the longer you stay, the more you will know you don't know."

The first problem facing public health workers in the Amazon Valley is the very vastness of the area and the tremendous scattering of the population. The Amazon and its tributaries drain an area of nearly 2¾ million square miles which is more than twice the area drained by the Mississippi and its tributaries, and represents an area equal

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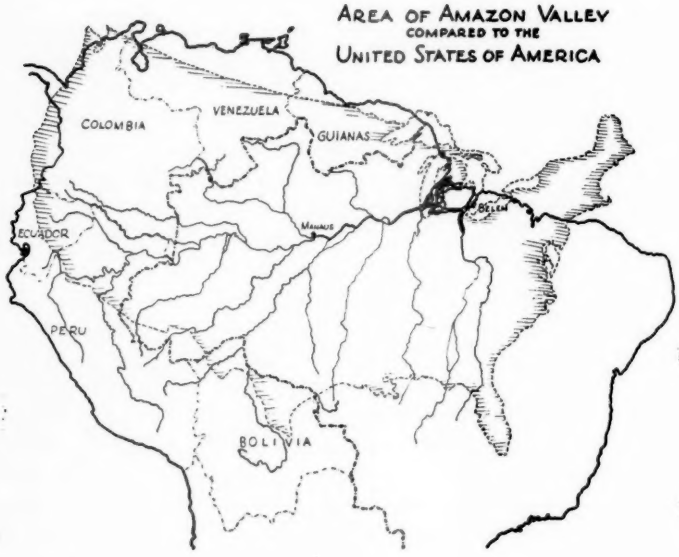
to approximately 90% of the entire United States. I have prepared a map (Fig. 1) which will give you some idea of



the size of this area as compared to the United States by using an equal area projection for the two regions. In placing the map of the United States over the map of South America, Detroit has been placed over the city of Belem, the capital of the Brazilian State of Pará. This brings Manaus, the capital of the State of Amazonas somewhere in the neighborhood of Lincoln, Nebraska. The west coast of the United States and the west coast of South America coincide to a certain degree, and it will be noted that several of the branches of the Amazon arise very close to the Pacific coast in the lofty ranges of the Andes. You will note that only half of this vast area drained by the many tributaries of the Amazon is located within Brazil. In this Brazilian half there is a population of approximately one and one-half million people. Although the other countries within the drainage area have

public health programs projected, or under way, I am planning to deal only with the problems in the Brazilian part of the Amazon Valley. Out of the one and one-half million people living in this area approximately one-half million live in cities. In the city of Belem there are more than 300,000 people; the population of Manaus approaches 100,000; two or three other cities have populations between 10,000 and 25,000; and there are several cities numbering a few thousand inhabitants. This leaves a million people living in what we would call small towns or strictly rural areas. Most of these live in isolated houses along the banks of the rivers. As one sails along these banks, one may see stretches of a mile or more without a house, then come upon several located a hundred yards or so apart, and then a half mile farther on there will be another isolated house, and so on. Excluding only the city of Belem, we find the population density of the Brazilian part of the Amazon Valley to average about one person per square mile, which is approximately that of the state of Nevada including its cities. It is as though in the whole area west of the Mississippi River, the only cities were Denver, Salt Lake City, and Reno, and throughout the rest of the area the population was scattered as thinly as that of Nevada.

When we consider the second great problem in this area, that of transportation, we begin to realize the importance of the tremendous size of the region. In this area, which is half as large as the United States, there are only 240 miles of railroad and less than a thousand miles of highways. Moreover, the nature of much of the land is such that it is virtually impossible to build either roads or railways. The influence of the ocean tides reaches hundreds of miles up all of the tributaries. Since the volume of the river system is so great that fresh water is carried far out to sea, the tides in these rivers are fresh water tides. The result is, however, that a very large proportion of the land is submerged either at every tide, or at the especially high tides coming at certain stages of the moon, or else it is so thoroughly saturated that construction of road beds would be an impossibility. Add

to this the fact that the lower half of the area is a veritable labyrinth of rivers and channels, dividing the land into many thousands of islands. To construct a long distance railroad or highway in the lower half of the valley would be nothing less than a bridge builder's nightmare. The main reliance in this area must be upon water transport. As compared with 15,000 miles of waterways navigable for commercial transport in the Mississippi River system, the Amazon has 27,000 miles of similar waterways and for boats of only six foot draft there are said to be more than 100,000 miles of channels. There are in this area a number of airports suitable for land planes. The airport at Belem is a stop on the east coast route to Rio, and not long ago saw hundreds of bombers passing through every day on the way to Africa. Aviation enthusiasts tell us that in the very near future we can leave New York, stop for gas at La Guaira on the north coast of South America, and then make our next stop at Manaus on the Amazon River, where we will take on enough gas to carry us in one hop to Rio. Undoubtedly other airports in the area will also become important as long distant travel begins to criss-cross the area. There are already local hydroplane services up and down the river, and the people of many of the towns of moderate size are accustomed to seeing the weekly plane land in the river in front of their village. These services will undoubtedly be extended, and the owners of large plantations may eventually have their private hydroplane services, but by and large only a few of the Amazon inhabitants will be able to travel by airplane in the foreseeable future.

To appreciate what this transportation problem really means in a public health program one must realize that in countries like these there are only a few private physicians and these all live in the large cities. A public health program must supply medical services to a very large part of the population, as well as those services which are considered to belong to the field of public health in our own country. Because of the difficult living conditions involved, the salaries of health officers in this region are kept reasonably

high as compared to the average income of physicians in Brazil, but when the cost of traveling by steamer is compared with the lowest rates that the airplane companies can foresee for the immediate future, it is evident that it will be cheaper for the health department to pay the health officers' salaries while they ride by the slow steamers to their posts and back to the centers for their necessary vacations, rather than to pay the higher fare necessary in airplane travel. The same economic situation exists to a greater degree with regard to the subordinate personnel of health departments. Since it frequently takes a month to go by boat from headquarters to some of the outlying health department offices, a considerable percentage of the health department personnel will always be traveling from one place to another, making necessary a much larger staff than would be required were rapid transportation available.

Where this difficult transportation problem really pinches is in the matter of supervisory personnel. It is especially in areas of scattered population that the responsibility for keeping a program active and up-to-date falls on the supervisory personnel, since the local personnel are apt to be younger men with less experience than those stationed in the large centers. In such an area as this with its very diverse problems, there is also a great need for having specialized personnel available on call to go to various points for the application of special studies and control measures whenever emergencies arise. At present, the health services have a fluvial division which is responsible for maintaining a small fleet of motor boats suitable for transporting such personnel to the points required when necessary. It is obvious that airplanes should be added to the facilities of this division if really prompt emergency service is to be given. When this will be financially possible cannot be foreseen.

Lack of adequate communication facilities is another problem. Various means of communication are available for use between the local health offices and the health department headquarters, but the people in the outlying districts have no means of communicating with the local

health offices other than making the trip in canoes; nor is the health officer able to inform the people of a community of any program that he may be instituting unless he or some of his staff make personal trips to notify the people living along the channels. Many of the health centers are in touch with headquarters by air mail and the services will increase soon. For sending the relatively voluminous monthly reports this service is now too expensive and ordinary boat mail has to be relied upon, which means that frequently the health officer's monthly report may be delayed two months in reaching headquarters. There are cable connections between many of the more important towns along the rivers. Breakdown of equipment is as frequent as in any system, but since the repair crews must come vast distances by boat, the interruption of services may exist for considerable periods. Government radio service is available in a few places and undoubtedly will be the solution of many of the communication problems.

The peculiar economic conditions of the Amazon basin create another problem for the health program. From an economic point of view the Amazon has always been treated by Brazil as though it were a colony of the parent country farther south. That is to say, it has been merely a source of raw materials and a market for traders' goods. For extracting the raw materials from the forests of the Amazon the laborer has been paid very little. The trader who traveled into the back country areas to barter for these products with manufactured articles instead of money, the middle man at at the larger ports where the products are collected for reshipment, and the transportation services have all exacted their profits. All too frequently these profits have been excessive. At the same time these traders and middle men have brought manufactured products from southern Brazil and have sold them to the people in the Amazon Valley, again making at least a fair profit. Now the characteristic fact about these profits is that they have not usually been reinvested in the Amazon Valley itself. When these middle men have accumulated enough to warrant, they have characteristically made a trip to south Brazil for a vacation and

there spent some of their profits and invested the rest. When they reach retiring age they customarily move to south Brazil for retirement.

Perhaps we should look at some figures regarding this movement of money and goods. The best single source for information of this type is the publication called "Brazil 1938," published by the Brazilian Institute of Geography and Statistics. The total exports and imports of the Amazon Valley in 1937 were not greatly out of balance, $17,000,000 worth of goods having been exported and $18,000,000 worth imported. Approximately half of the exports went to other parts of Brazil and half to other countries, but the imports from other parts of Brazil equal $15,000,000 as compared to $3,000,000 imported from other countries. Since the exports to other countries were handled for the most part by Brazilian companies with headquarters in south Brazil, it seems obvious that there is a favorable balance of credit going into the rest of Brazil at the expense of the Amazon Valley.

Other evidence of the type of economy existing in the region can be found in a study of the report on revenues and disbursements during the years 1935, 1936 and 1937. The total federal, state, and municipal revenues of the Amazon region for this three year period amounted to 15¼ million dollars, whereas the disbursements were 13½ million, leaving 1¾ million, or 11% of the revenue unaccounted for. The reports show that the state and municipal revenues and disbursements approximately balance each other, and that the discrepancy lay almost wholly in the federal revenues and disbursements. It is quite possible that these figures do not mean exactly what they seem to on the surface, but unofficial information which I have obtained from Brazilian government sources indicate that this would be a fair example. It is only fair to point out, however, that during the three year period the discrepancy decreased in amount each year, and that these conclusions apply to the pre-war period.

The amount of money spent for public health and education is most readily available for the year 1935. It should be

again pointed out in connection with these figures, that public health in such an area includes nearly all of the medical and hospital services of the area. In that year there were listed for this region 61 hospitals supported by federal, state, or municipal funds, and 25 private hospitals. During the year "hospital assistance" was given to approximately 29,000 in-patients and 197,000 out-patients, and the public disbursement for "medical and health services" totaled $338,000, or approximately 22 cents per capita. Since virtually all of the hospitals are in the larger cities it seems evident that nearly one million people had virtually no access to medical or hospital services. The distribution of educational services is not quite so uneven, since schools do exist in the smaller communities. In all, 1724 schools were reported for 1935, and the public expenditure for education total something over one-half million dollars or 35 cents per capita. For the whole of Brazil the disbursements for medical and health services amounted to 24 1/3 cents per capita and for education 45½ cents. In view of the possibility of inaccurate estimate of population for the Amazon region, the disagreement is not great.

The principal point of argument supported by these figures seems to be that goods and credit were taken out of the region to a much greater extent than the return of services to the region. Under some of the philosophies of government now popular one could argue that in this backward region, it is not possible to assess sufficient taxes to support the necessary public services, and the more fortunate regions of the country should contribute to these areas rather than reap a profit from them.

As a matter of fact, some such philosophy has been evident in the action of the government during the war period. Stimulated by the Office of Inter-American Affairs of the United States Government, an organization known as Special Health Services, or S. E. S. P., was created. Independent of the State Health Departments in this region, but co-operating with them, and supplementing their efforts, S. E. S. P. has attempted to devise and demonstrate methods of

providing more adequate health services to this region. The cost of this program is being shared on a five year basis by our government and the government of Brazil. Our contribution is a part of the good neighbor policy which has had so much criticism both pro and con. I shall not attempt to state my opinion with regard to this policy, and it certainly is too early to assess the true value of the program as a whole or of its parts. Our motives as a nation in making such a contribution to this region were essentially humanitarian. The reasons for taking action at this particular time were, however, in part military in that protection of the health of the workers aided in speeding the flow of essential products, and in part commercial in that a healthy population will be a better basis for more active trade in the post-war period. The Brazilian government is now contributing more largely to this backward area and there is every indication that a strong sentiment exists for the continuance of such contributions after this coöperative program between the two governments has been completed.

In the long run the future of the region depends upon its own economic development. On this point opinions of experienced observers seem to fall into two classes. On one hand a brilliant future is forecast for the region. It is claimed that regardless of other world rubber developments, the Amazon rubber will long hold its own place in the world markets. It cannot be disputed that this valley contains the greatest hardwood forest reserve in the world. The demand for oils, fats, resins and other products of the forest is expected by these people to increase because their properties enhance the qualities of synthetic plastics. The large pre-war trade in Brazil nuts is expected to be renewed on a greatly expanded scale. Plantation development of several crops on a large scale is prophesied. Henry Ford has long had a rubber plantation on the Amazon and has maintained the experiment in spite of the indifferent success it has been commercially. Another American industrialist who is reported to have acquired millions of acres in the valley is cited as the forerunner of a trend. The successful cultivation of jute in the

valley is expected to lead to the development of large scale planting of fiber crops. I was shown experimental stands of plants yielding a very much higher percentage of the valuable insecticide, rotenone, than it is possible to obtain from the average wild plant. And so straw after straw in the wind can be pointed out.

On the other hand equally experienced observers have more pessimistic but just as positive views. Rubber has a temporary future, they say, and even the oils, waxes and resins will soon be duplicated from cheaper sources. Harvesting the timber can never become an industry. There are no stands of timber composed of one, or even of a few types of trees. The desirable species are represented by single specimens scattered among hundreds of other species of little or no market value. To fill an order for any species, trees must be cut here and there in territories covering several hundred miles. The clearing of areas big enough to fell one of these forest giants is a prodigious and thankless task when only the one tree is of value. In much of the valley the ground is too soft to support wheels and other physical conditions prevent easy skidding. Even when the logs reach the river bank they cannot be floated out. It is hard for us to believe our eyes when we see wood which will not float. I was only satisfied when I had selected a thoroughly dry piece, threw it in the river, and watched it sink like a stone. All of these reasons are marshalled to show that lumbering can never be a large scale industry in the Amazon Valley.

Plantation agriculture is likewise discounted. Brazil nut trees take fifty years to come into bearing and even though they will then bear for another fifty years, where will the money for such long time investment be found? The difficulty of clearing the jungle and keeping down the tropical growth is mentioned. Certain it is that individual farmers cannot hope to clear their own land as in the pioneer days of our country. Much of the soil of the valley, except in the lower alluvial regions, is said to leech rapidly when it is exposed to the sun upon removal of the forest growth. Plant diseases are, of course, an obstacle in a warm humid region. The

indolence of the labor now available and the difficulty of acclimatization of imported labor are factors whose importance is still debatable. Thoroughly scientific evidence on these various points does not as yet seem to be available. Certainly to overcome the hazards of the region, large scale production will have to perform wonders, but miraculous changes have been brought about in other difficult places, and it seems best to reserve judgment.

The impact of politics on the economic life of the valley is equally important but can be forecast even less satisfactorily. It is claimed that the overlords who once dominated the area have now been eradicated, and sound commercial policies instituted. The government is said to be awake to the strategic value of the area and to realize that it must be developed to the extent of improving the welfare of the inhabitants. Others claim that the prospects for agriculture are so much better in other vast undeveloped areas of Brazil, that its future can only be based on the value of the forest products to be extracted. They say it is too far from the rest of the country to be of much interest to the inhabitants of the more densely populated regions of the south where most of the votes are cast. It is even more obvious that this answer too lies in the future.

Let us turn now from these external problems of a public health program to its internal problems. In addition to the problems faced by health departments in our own country, there are many difficulties peculiar to the tropics. The tropical diseases as a group are generally more susceptible to control on a mass scale rather than through medical attention to the individual. Malaria is widespread in the valley and it is not entirely clear just what represents a sound control policy within the economic structure. Experiments with residual sprays in houses were being projected when I was there. Drainage and other types of major construction seem appropriate only in a few places in this region of intermittent flooding. In this as in other connections, the vast population scattered thinly along the many river banks present very difficult problems. Fortunately recent studies have shown that filariasis and the accompanying elephantiasis

are present only in the city of Belem and not throughout the valley as indicated by previously published maps. Its eradication would seem entirely possible. Success would depend upon improvements of drainage, sewage disposal and housing, all of which are much needed in this old city, but are expensive to attain. Infection with other worm parasites present no problems different from those of other tropical regions, but again are bound up with the need for better housing, nutrition and general economic conditions. Yaws and leishmaniasis are prevalent and are problems occupying much of the attention of the medical health officers. Nutrition must be improved and considerable attention is being given to the problem. A special food production program showed that the valley can raise its own food stuffs of a satisfactory quality, but the financial support, incentive, and direction must still be supplied. In a region where one is so greatly impressed by the presence of so much water, it is strange to see the people eating imported codfish. They do salt down local fish to some extent and the isolated families living along the banks probably catch fish for themselves. Only twice in a twelve day trip was fresh fish located by the captain of our launch and then none appeared on our table, and I doubt if any of the crew aside from the captain had a taste. At one town we saw people practically fighting to buy strings of fish handed up from men in canoes along the waterfront. I was told that it was an exception to see fish sold in towns at places other than at the town market because the law usually required it to be sold only there so that federal, state and local taxes could be imposed. Two reasons were given me for the scarcity of fish in these markets. One was the fact that these taxes took half of the money received for the fish, and the other that since jobs created by the war programs paid so much better, the fishermen had largely left their trade. Some tropical fruits are available in the smaller places, but obviously the general population does not consume enough of them. Vegetables containing protective elements are rarely seen. The new health centers have an active garden program. At each center there will be a demonstration garden to show

the people how to raise vegetables in spite of the torrential rain, burning sun, army ants and other problems. The gardens will be big enough to make possible a supply for the use of health educators in developing a taste for them. In one town I was surprised at the number of plots I could see in the little front yards as I peeped in the cracks of the fences. It was here too that we obtained from the health center garden the only fresh vegetables of our twelve day trip. This type of development is realistic and independent of economic development, since the seeds are distributed free.

There is no time to discuss the many other health problems such as water supply, rural sanitation, prenatal and postnatal training of mothers, all of which are not greatly different from those of other tropical regions. There are, however, certain problems which have interesting elements peculiar to this region. One of these is the personnel problem which is acute, but is being faced valiantly and with an eye to the future. We shall consider only the medical and nursing problems as they are the most concrete, and are typical of the problems relating to all kinds of personnel. The present program aims at providing a measure of health service to thirty-one towns located strategically throughout the valley. Nearly all of these represent places where living conditions are primitive as judged by any urban standards whatever. Medical graduates will accept temporary appointment to these posts for the experience, but to warrant the specialized training necessary for satisfactory service, relatively permanent assignments are indicated. Therefore, the taking of families to these places becomes important. Graduates of the medical schools in southern Brazil and their wives find even the state capitals in the Amazon Valley to be difficult, and the isolated regions in the valley are possible only in the few cases where man and wife have a pioneering, missionary spirit. The strain is not so great on the men whose homes are in the Amazon Valley and who have had their medical education in Belem. Even though this training is not of the best according to Brazilian standards, it appears that the only answer is to take young men of the region, fresh from

the local school, give them the necessary additional training, and hope that if they start both their careers and family life in these places they will become sufficiently adapted.

Nursing education has been a problem throughout much of Latin America where career women have been unknown until recently. The families whose daughters receive the basic education necessary to enter nursing feel that the work is too much like servant's work. Add to this difficulty the problem of living in these isolated communities and the common opinion of the inhabitants that a single woman coming to work in a community certainly must be one with less than the highest moral standards. Progress has been made in the face of this seemingly insoluble problem. With a community education program to create the correct attitude in the minds of the people, locally educated girls have been hand picked for work in their own communities. They go to one of the smaller cities of the region for their training course so their attention is not diverted by the wonders of the large cities, and the home folks do not feel that they have been too far removed from their own region. They return home, however, with considerable prestige and are furnished with a practical but distinctive uniform to mark them as a professional class. To leave the way open for the later introduction of professionally trained public health nurses, these girls are not called nurses, but *visitadoras* or visitors. In a small health center two girls will divide the community between them. One will visit homes in her section on alternate days while the other stays in the health center to assist the doctor in the clinics. On the other three working days each week the other girl will be outside. When in the clinic each girl will be ready to greet any patient she may have referred in on the previous day. She can likewise tell the mother who has just received from the doctor a new formula for her baby that she will call tomorrow and show her how to prepare it. This plan of alternate schedule and definite area assignments will also be in effect in larger centers and everywhere there will be emphasis on midwife training classes. Thus there is being laid a foundation for more complete

nursing services which may be developed later on in this program.

Then there are peculiar training problems to be faced. A hint of some of them has been given in discussing the personnel problems. Facilities for training laboratory technicians, sanitarians, malaria inspectors, foremen for privy building programs and many other types of workers have to be provided. The training center for *visitadoras* has been established at a small city where a teaching hospital is being built for the purpose. The teachers are trained nursing instructors from south Brazil. The training school for other classes of personnel is located in Belem. Many of the key positions are well filled by men trained in schools of Public Health in the United States or in Sao Paulo. Others are occupied by temporary appointees on leave of absence from other posts until new men can be developed for the places. A large number of people pass through the out-patient department of the training hospital at this center. From them the cases suitable for teaching purposes are selected to enter the hospital, and the rest sent to the large general hospital located in the same grounds. A model health center suitable for training purposes is being erected in a nearby town and a training center for laboratory technicians has been functioning in connection with a public health laboratory which serves the program of the Belem region.

These then are some of the problems, and an indication of how they may be solved. A great deal of money is being spent to find the correct answers to many of the questions we have raised. The advance of public health services in the region will depend for the most part on the future economic expansion, which is in itself another problematical matter. Certain it is that we as the largest nation in North America have close ties with the largest nation in South America, and we will follow with great interest the future development of the region not only because of its impact on our own economy, but because of our romantic feeling regarding this wild wonderland of the Amazon.

ANTI-RICKETTSIAL ACTIVITY OF PARA-AMINOBENZOIC ACID (PABA):

EFFECT OF PABA ON EXPERIMENTAL SPOTTED FEVER*

LUDWIK ANIGSTEIN AND MADERO N. BADER

The almost miraculous effect of sulfonamides on most bacterial infections led research workers to investigate the possible therapeutic effect of these drugs on rickettsial diseases. It soon became evident that the effect of sulfonamides on typhus and spotted fevers in man and laboratory animals is far from beneficial. Sulfapyridine and prontosil were tested by Topping (1939) on experimental typhus and spotted fevers with the result that these drugs were found not only of no value but harmful to the host animal. Similar studies by Steinhaus and Parker (1943) who used sulfathiazole, sodium sulfathiazole, sulfaguanidine, sulfadiazine in experimental spotted fever led to the same conclusion. In the hands of Fitzpatrick (1945) sulfapyridine and sulfathiazole were contraindicated in experimental spotted fever since deaths occurred in the treated animals sooner than in the controls.

The last two reports were preceded by investigations of Snyder, Maier and Anderson who initiated their studies in 1941 and found that the sulfa drugs enhance the multiplication of rickettsiae in infected animals. In sulfa treated animals the infection was more severe than in the control groups. (Report to the National Research Council, Dec. 1942.) This adverse effect of the sulfa drugs had inspired Snyder, Maier and Anderson to attack the problem from an entirely different angle. Their concept was based on the premise that the "antagonism between the sulfa drugs and p-aminobenzoic acid on bacterial growth might be present in rickettsial infections in the reverse directions." This logical assumption was the starting point of investigations of a possible beneficial

*From the Department of Preventive Medicine and Public Health, The University of Texas School of Medicine, Galveston, Texas. Received for publication March 20, 1946.

effect of p-aminobenzoic acid on rickettsial infections and, as it seems, the opening of a new chapter in chemotherapy of this group of diseases.

Preliminary experiments on mice fed with p-aminobenzoic acid (PABA) a few hours or 2 days prior to infection with murine typhus gave encouraging results: only 2 of 35 controls survived, as opposed to 27 fed PABA (total 34). In conclusion of their report Snyder, Maier and Anderson made the following statement: "These results suggest that further investigation of the effect of para-aminobenzoic acid and closely related compounds on typhus fever is warranted."

The opportunity of a clinical trial presented itself during the epidemic of louse-borne typhus in Cairo, Egypt, in 1943 and 1944. The usual amount of the drug given by mouth was 2 gm. in 25 cc. of 5% sodium bicarbonate solution every 2 hours. Under these conditions the blood level of free PABA was kept between 10 and 20 mg. per cent. The treatment was continued until normal temperature of the patient was attained. The average total amount of PABA for each case was about 127 gm. The comparison of PABA treated patients with the untreated group was very impressive; whereas the mortality from typhus among the untreated 44 patients in the Fever Hospital was 18%, none of the 17 PABA patients died. A definite lessening of the severity of typhus as well as a considerable shortening of the fever duration were noticed in the treated group (Yeomans, Snyder, Murray, Zarafonetis and Ecke, 1944).

Meanwhile, an extensive search of anti-rickettsial agents was in progress in England where Andrewes, King and Van den Ende (1943) in testing more than 164 compounds found only three of anti-rickettsial activity. These authors were also able to demonstrate a slight beneficial effect of maximal doses of para-aminobenzoic acid given to mice infected with typhus by intranasal route. It is of interest to note from a later report of Andrewes, King, Van den Ende and Walker (1944), that two compounds related to sulfonamides (designated as V 147 and V 186) but not inhibited by p-amino-

benzoic acid were found to have a definite beneficial action on experimental murine and louse-borne typhus in mice.

Recent experimental work on anti-rickettsial activity of p-aminobenzoic acid is mainly based on its action on rickettsiae cultivated in embryonated eggs. It was shown by Hamilton, Plotz and Smadel (1943, 1945) that the growth of typhus rickettsiae in the yolk sac of the developing chick was markedly inhibited by p-aminobenzoic acid when maximal dosages of the drug (2-4 mg. per egg) were injected. In addition, a prolongation of the survival time of infected chick embryos treated with PABA was noted.

A rickettsiostatic activity of PABA was also established by Greiff, Pinkerton and Moragues (1944) in their experiments with murine typhus rickettsiae cultivated on yolk sacs of developing eggs. Mice infected with murine typhus and fed with PABA by mouth (3% in food) survived at a rate approaching 100% as contrasted with a survival rate of zero in controls.

These significant observations on the activity of PABA on typhus rickettsiae led the authors of the present report to extend the investigations to experimental spotted fever (Anigstein and Bader, 1945). Evidence was offered by Hamilton in his report (1945) on the inhibitory action of PABA on the growth of Rocky Mountain spotted fever rickettsiae cultivated in embryonated eggs. It is of interest to note that in Hamilton's experience the inhibition by PABA was in many cases more striking on the rickettsiae of the spotted fever group than was obtained with typhus. On the other hand, it was found by the same author that the rickettsiae of Q fever and tsutsugamushi were apparently unaffected.

In contrast to the negative results in egg cultures of tsutsugamushi rickettsiae Snyder and Zarafonetis (1945) and Murray, Zarafonetis and Snyder (1945) were successful in preventing death of gerbilles infected with tsutsugamushi and treated with PABA. The results were, however, dependent on the method of administration of the drug.

In spite of the promising results in animal tests PABA has so far entirely failed in tsutsugamushi disease in man (Lewthwaite, 1945).

Clinical application of the PABA effect on experimental spotted fever (Anigstein and Bader, 1945) and its inhibitory action on the growth of spotted fever rickettsiae in chick embryos (Hamilton, 1945) was made for the first time by Rose, Duane and Fishel (1945). These authors have treated a spotted fever case with PABA beginning with the fifth day of illness, the dosage being 2–2.5 gm. of the drug in 5% solution of sodium bicarbonate given orally every two hours. Following the first 24 hours of therapy with PABA clinical improvement was evident and continuous with a rapid decline of fever and a rapid and uneventful recovery. The authors admit that they cannot conclude from a single case that these effects were directly attributable to the drug, however "their relationship suggests that such was the case."

At the time when our own study on the effect of PABA on experimental spotted fever was initiated, the only rickettsial infections in which the efficiency of this drug was reported were murine and louse-borne typhus fevers. The possible action of the drug on other rickettsioses was obviously of interest and with this objective in mind spotted fever was chosen. The clear-cut clinical response of the guinea pig to the infection, the regular and short incubation period followed by the abrupt rise of body temperature, the well defined fever chart, the specific scrotal lesions and, finally, the invariably fatal issue were particularly suitable for comparison with any deviations resulting from the action of the drug. On the other hand, the fulminant course of the infection gave little promise to the investigator in challenging the drug with this severe test.

Material and Methods

Guinea pigs of 450–600 gm. body weight were infected with a highly virulent Rocky Mountain spotted fever strain of tick origin kindly supplied by the Rocky Mountain Laboratory, U. S. Public Health Service.

In all transfers the infectious material—spleen suspension in skimmed milk—was injected intra-abdominally. On the whole, a remarkable regularity in the manifestations of the disease was noted throughout the numerous transfers with only occasional deviations from the typical course. In the great majority of the control series the incubation period was 72 hours, while in sporadic instances short incubations of 48 hours were observed. Very rarely was the fever attack preceded by 5-6 days incubation. The height of the abrupt attack of fever was usually reached on the third or fourth day fluctuating between 40° C. and 41° C. for another day or two and then subsiding within the next two or three days. The average duration of fever in the controls was 5-6 days with extremes of 3-8 days. Atypical fever such as in guinea pig 2059 (see Chart 3) was only once recorded.

Whenever available, male guinea pigs were used in which typical scrotal swelling with purple discoloration and frequent necrosis of the scrotum was noted. The fatality rate of the untreated guinea pigs was practically 100 per cent regardless of the duration and intensity of fever.

Oral administration of PABA (Eastman Kodak Co.) was adopted, its daily content in food ranging in various series from 1-3 gm. per guinea pig. These amounts of the PABA powder were uniformly mixed with 100 gm. of coarsely chopped raw carrots and cabbage supplemented with Purina Chequers rabbit chow pellets as a source of protein. It was noted that the increased protein intake adds to the efficiency of the drug.

In testing various amounts of PABA it was found that while food containing 1 per cent of the drug had some beneficial effect, the concentration of 3 per cent of the drug was either refused by the guinea pig or had an adverse effect. On the other hand, diet containing 2 per cent of PABA was well tolerated.

Each guinea pig was kept in a separate cage so that the diet intake could be checked every 24 hours. Some guinea pigs were sluggish eaters or refused the PABA diet entirely.

In these cases no effect of the drug on the course of the infection could be expected.

Although the work was concentrated on p-aminobenzoic acid, its conjugated acetylate compound was in several experiments tested against spotted fever. A preliminary trial was also given to such agents as dl-methionine, thyroxine and thiouracil.

Results

Previous reports of various authors on the anti-rickettsial activity of PABA are chiefly based on observations of chick embryos or mice infected with typhus rickettsiae (Snyder, Maier, Anderson, 1942; Greiff, Pinkerton and Moragues, 1944; Hamilton, Plotz, Smadel, 1945). Hamilton (1945) in using developing eggs extended the observations to the rickettsiae of the spotted fever group and also to the organisms of "Q" fever and tsutsugamushi. Finally, gerbilles were recently used for testing the effect of PABA on experimental tsutsugamushi disease (Snyder and Zarafonetis, 1945; Murray, Zarafonetis and Snyder, 1945). Since no guinea pigs were previously used for experiments with PABA its dosage was rather arbitrary. From the experience in the treatment of typhus infection in man and in mice, it was clear, however, that large amounts of PABA are required to achieve satisfactory results. Murine typhus infection was successfully treated when PABA was added in a concentration of 3 per cent to the food (Greiff, Pinkerton, Moragues, 1944).

The first series of guinea pigs in our own study was fed with 1 per cent PABA in diet from the first day of infection with spotted fever rickettsiae over a period of seven days. Of six treated animals three developed typical fever simultaneously with the controls; in one guinea pig the fever was delayed for three days; there was one survival. In the two remaining guinea pigs of this series the temperature was normal for 14 days observation except for two slight elevations each of one day duration. Both guinea pigs were later

reinoculated with spotted fever without showing any febrile reaction, and were released immune. The results of this test although not entirely favorable were nevertheless significant. It was shown that on two occasions a low dosage of PABA did suppress the clinical symptoms of the otherwise fatal infection.

In further experiments the daily dosage of PABA in diet was increased to 2 gm. per day, otherwise the mode of administration was the same. In the first group of this series (see Chart 1) PABA treatment was begun 24 hours prior to spotted fever infection and continued for the following eight days. None of the four test guinea pigs developed clinical spotted fever, however, one (No. 2050) showed an abrupt elevation of temperature at the end of the usual three day incubation which subsided to normal the following morning. There were two more abortive attacks three and five days later followed by a prompt recovery of the animal. Slight and fleeting elevations of temperature were registered in the remaining three guinea pigs of this series, one of them (No. 2051) showing two short fever attacks, the relapse following a four day interval. Due to accidental perforation of the rectum by the thermometer this guinea pig died, otherwise the three PABA treated guinea pigs recovered. The next experiment included ten guinea pigs, four of which were controls. As shown on Chart 2, one control animal developed a rather atypical fever after a long incubation of 6 days, while in the other three controls spotted fever was characteristic and severe.

All the control guinea pigs developed typical scrotal lesions, three of them died, while one (No. 2056) was killed for transfer.

As compared with the clear-cut and the fatal issue of the infection in control animals, a striking difference in the response of the test guinea pigs was observed (Chart 2). While slight fevers of one and two day duration coinciding with the end of the incubation period of the controls were registered in three guinea pigs, the body temperature of the other three test guinea pigs remained normal over 15 days

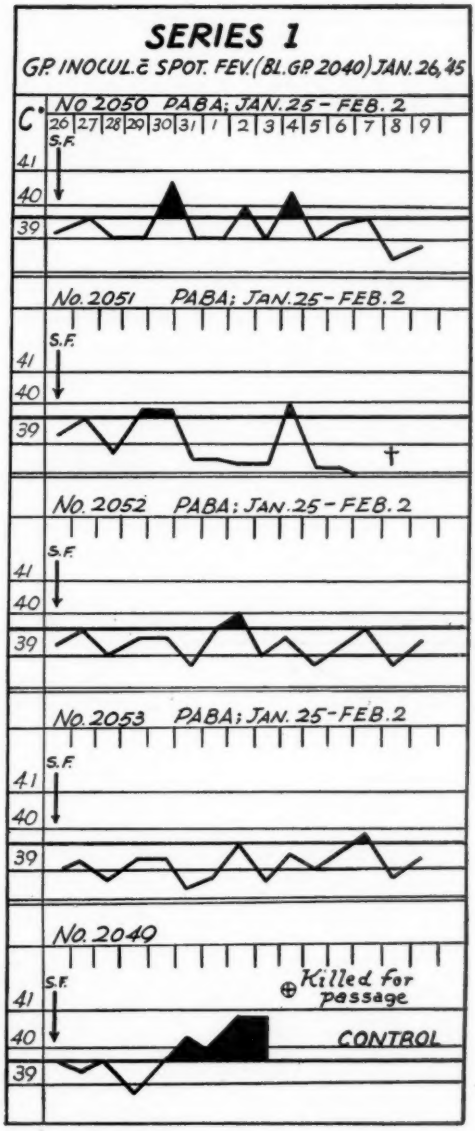

SERIES 1
GP. INOCUL. & SPOT. FEV. (BL. GP. 2040) JAN. 26, '45
C°
No. 2050 PABA; JAN. 25 - FEB. 2
26 27 28 29 30 31 1 2 3 4 5 6 7 8 9
S.F.
41
40
39
No. 2051 PABA; JAN. 25 - FEB. 2
S.F.
41
40
39
†
No. 2052 PABA; JAN. 25 - FEB. 2
S.F.
41
40
39
No. 2053 PABA; JAN. 25 - FEB. 2
S.F.
41
40
39
No. 2049
S.F.
41
40
39
⊕ Killed for passage
CONTROL

Chart 1.

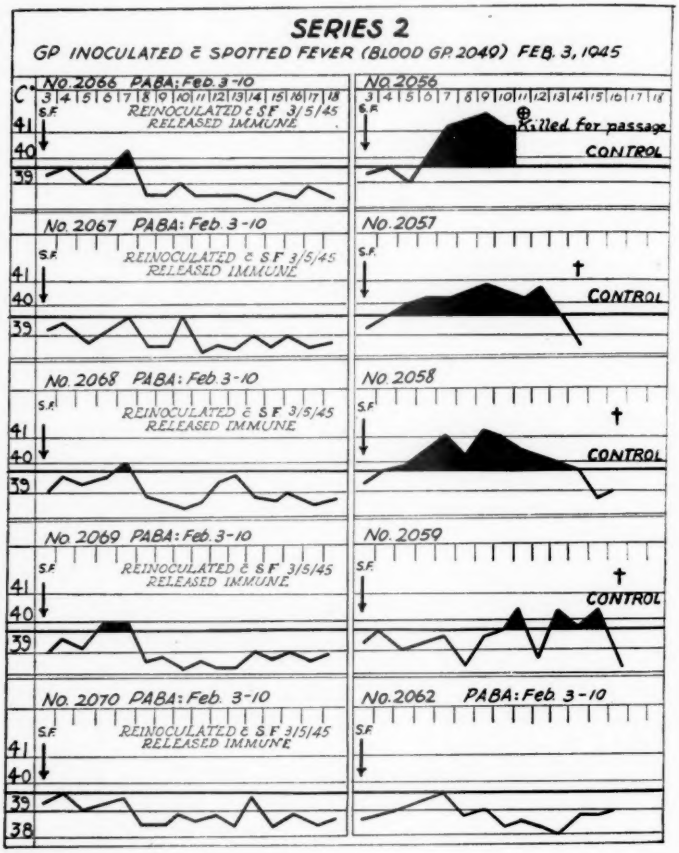


Chart 2.

observation. In none of the test guinea pigs, all of which eventually recovered, were scrotal reactions observed. The surviving animals were reinoculated intra-abdominally one month later with the routine transfer spotted fever material and all showed complete immunity.

Experiments in this direction were continued with 2 per cent PABA concentration, the only variable being the duration of the treatment and the timing of the drug administration

with the infection. The actual intake of PABA by the guinea pig could be evaluated only approximately due to a rather erratic appetite which diminishes during the progress of the disease.

On the average, 50-70 gm. of food were taken by a single guinea pig in 24 hours which is equivalent to 1-1.4 gm. of PABA, although during the incubation period the total of

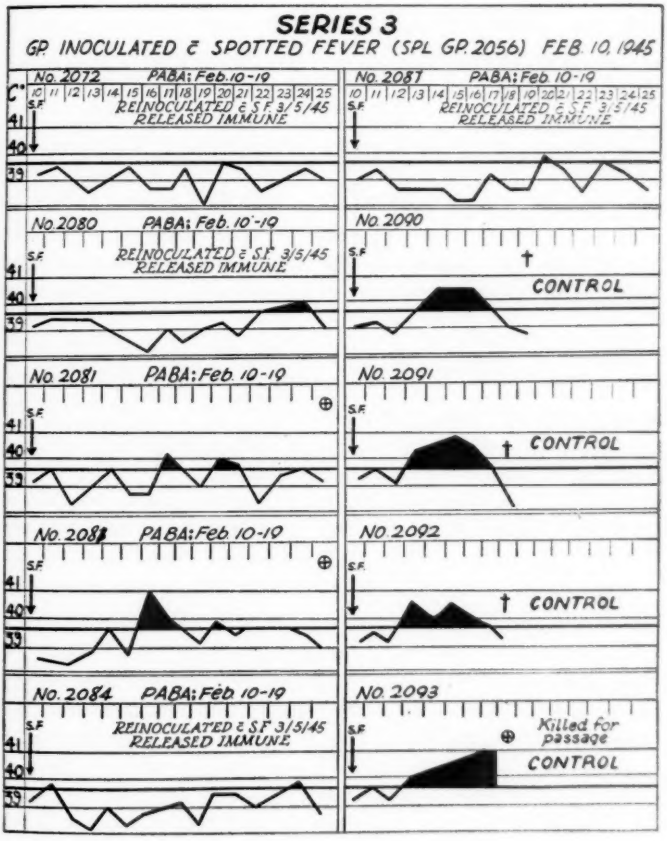


Chart 3.

100 gm. containing 2 gm. of PABA were eaten per day by many guinea pigs.

Favorable results were obtained in Series No. 3 of six treated guinea pigs as compared with the four controls (Chart 3). In this group the PABA administration begun on the day of spotted fever injection was continued daily for the next nine days. All untreated animals reacted with typical fever, scrotal lesions and died, except one which was sacrificed for transfer. In sharp contrast to these results a significant rise in temperature was recorded only in one guinea pig (No. 2083, Chart 3) on the sixth day after inoculation. The abrupt fever attack which reached 41° C. subsided however the following morning, and the temperature, showing a slight fever relapse two days later, remained normal. The fever reaction of guinea pig 2081 is characterized again by an abortive attack followed two days later by a relapse (Chart 3). Except for two guinea pigs killed at the end of two weeks observation, the remaining four recovered animals were re-inoculated with spotted fever rickettsiae and proved to be immune.

Favorable results were also recorded in Series 4 and 5 (Charts 4 and 5) with the exception of the PABA treated guinea pig No. 2100 which died. Two guinea pigs (No. 2101 and 2178) reacted with abortive fever attacks while eight test guinea pigs remained afebrile during 17 days observation. They were all reinoculated 4 or 6½ weeks later and released immune to spotted fever. On the other hand, the untreated guinea pigs developed typical and fatal spotted fever.

As evidenced by the clear-cut and fulminant character of spotted fever in the untreated guinea pigs a definite and striking change was noticed in the clinical response of guinea pigs exposed to the same infection but treated with PABA. This change consists in either complete absence of detectable clinical symptoms or in their reduction to abortive fever attacks in the PABA treated series followed by recovery. These phenomena were due to the action of PABA administered from the very beginning of the spotted fever infection or preceding it by 24 hours.

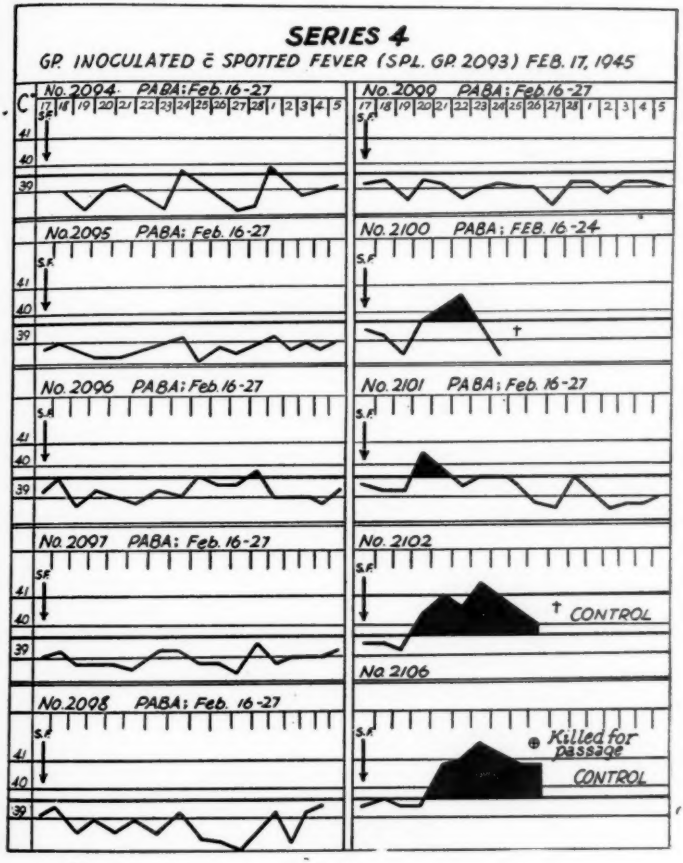


Chart 4.

In analyzing the temperature charts of the PABA treated guinea pigs the occurrence of abortive fever attacks and of relapses perhaps deserves attention. It was noted in several instances that the first fever attack usually coincided with the end of the incubation period of the untreated controls. This was probably due to the temporary gain of the invading and multiplying rickettsiae over the suppressive action of the drug. An interference of specific antibodies at this early stage

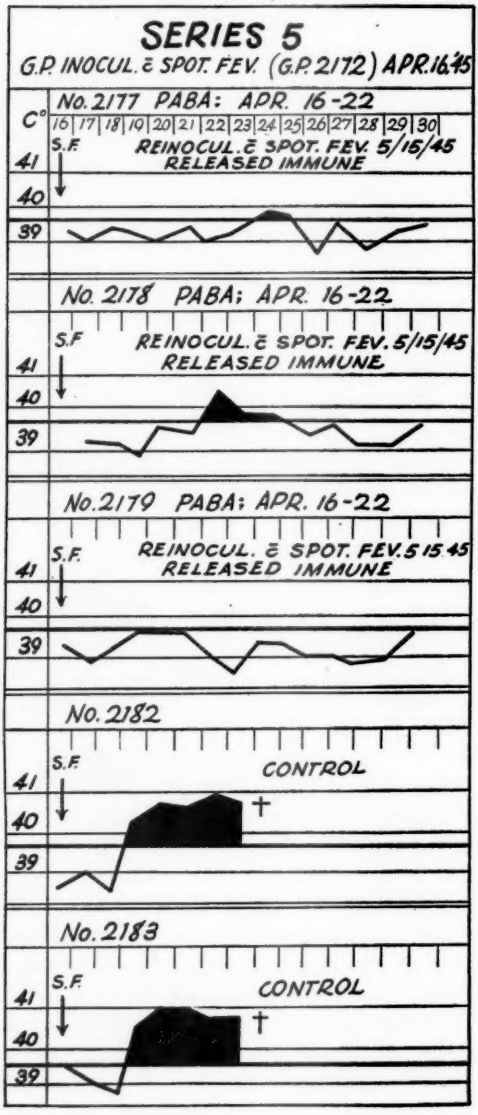

SERIES 5
G.P. INOCUL. & SPOT. FEV. (G.P. 2172) APR. 16-45
No. 2177 PABA: APR. 16-22
C°
16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
S.F.
REINOCUL. & SPOT. FEV. 5/15/45
RELEASED IMMUNE
41
40
39
No. 2178 PABA; APR. 16-22
S.F.
REINOCUL. & SPOT. FEV. 5/15/45
RELEASED IMMUNE
41
40
39
No. 2179 PABA; APR. 16-22
S.F.
REINOCUL. & SPOT. FEV. 5 15 45
RELEASED IMMUNE
41
40
39
No. 2182
S.F.
CONTROL
41
40
39
No. 2183
S.F.
CONTROL
41
40
39

Chart 5.

of the infection could hardly be expected. In other cases a late attack or relapse was recorded simultaneously with the withdrawal of PABA from the diet. It is possible that these ephemeral reactions were at the later stages of the infection influenced by specific antibodies and that after the path was paved by the suppressive action of the chemical agent the pathogenic activity of the rickettsiae was arrested by the defense mechanism.

The above findings and considerations corroborate the observations of Yeomans, Snyder, Murray, Zarafonetis and Ecke (1944) who have noted in half of their typhus patients treated with p-aminobenzoic acid secondary febrile periods after the drug was withdrawn.

While the combined action of PABA and the defense mechanism protected the guinea pigs from clinical symptoms and death, it did not prevent the development of pathologic changes. The post-mortem of some of the afebrile and recovered "treated" guinea pigs showed in most instances an enlarged, dark and friable spleen, as in spotted fever. In addition, pneumonitis accompanied by minute petechiae in the lung tissue was frequently observed. Furthermore, the presence of virulent rickettsiae in those animals was demonstrated by passage of the spleen emulsion to susceptible guinea pigs which developed typical spotted fever and died. Consequently, the absence of symptoms in the successfully treated animals is only an apparent one, similar to the type of infection as first observed by Charles Nicolle in rats and sometimes in typhus infected guinea pigs and designated by him as "infection inapparente." It may be added that in the experience of Greiff, Pinkerton and Moragues (1944) "the addition of para-aminobenzoic acid to the food makes the disease (typhus) in mice inapparent, as it is in the normal rat."

Regardless of the mechanism and nature of the protective action of PABA it was of interest to explore its effect when the treatment of guinea pigs was delayed for certain periods beyond the time of infection.

For this purpose four groups of guinea pigs were infected with spotted fever. One batch of four guinea pigs served as control, while each of the three remaining groups was started on diets containing 2 per cent PABA 24 hours, 48 hours and 72 hours after infection. The PABA treatment was shortened to six days, after which period it was replaced by normal diet. In the group which received PABA 24 hours after infection one guinea pig developed regular spotted fever and died, another had an abortive attack on the sixth day after inoculation then became afebrile and recovered. The other two did not show any symptoms and also recovered. All three were reinoculated afterward with spotted fever and released immune.

Of four guinea pigs in which the PABA treatment was delayed by 48 hours two remained afebrile and recovered while the other two died from spotted fever. Only one guinea pig remained afebrile and recovered of four treated with PABA 72 hours after infection. It can be seen therefore that the critical delay seems to be 48 hours. These results are comparable with those reported by Hamilton, Plotz and Smadel (1945) on embryonated eggs infected with typhus rickettsiae and subsequently treated with PABA.

In view of the progressively diminishing protective value of PABA during the 72 hours incubation period, its actual curative effect could hardly be expected. This proved in our experience correct. The administration of the drug on the first day of fever in guinea pigs gave invariably negative results. In this connection the spectacular success achieved by Rose, Duane and Fishel (1945) in the human case of spotted fever with PABA treatment is worth emphasizing.

Attempts were also made to "pretreat" guinea pigs with PABA before infection. Six guinea pigs were fed with 2 per cent PABA diet for five consecutive days after which they were infected with spotted fever and fed on normal diet. All of them developed typical spotted fever simultaneously with the untreated animals, with no survivals.

Since the original idea of using p-aminobenzoic acid in typhus fever therapy was based on its antagonism to sulfa

drugs (Snyder, Maier, Anderson, 1942) the question arises whether other sulfonamide-antagonists may possibly act as rickettsia inhibitors. Methionine is listed by Henry (1944) as sulfonamide-antagonist, although it is less active than PABA. Its metabolism is almost as obscure as that of PABA, but evidence was obtained that methionine stimulates the synthesis of active respiratory enzymes (Henry, 1944, p. 56), in other words it may be classified among the enzyme activators. It was felt therefore that the trial of methionine might prove of interest.

For this purpose dl-methionine (Eastman Kodak Co.) was injected subcutaneously in amounts from 0.05-0.1 gm. daily for five consecutive days to each of six guinea pigs prior to the infection. In another series the treatment began with the incubation period and was extended over 3 days of fever. There was no change whatsoever in the treated animals as compared with controls with no survivals.

Other agents influencing metabolic processes such as thyroxin and thiouracil were tested in a similar way but none of them proved of beneficial value on experimental spotted fever.

Of PABA derivatives its acetylate form—acetyl-p-aminobenzoic acid was tested by feeding guinea pigs similarly to the PABA procedure. No influence on the course of the infection was recorded. These results can be compared with those obtained by Hamilton, Plotz and Smadel (1945) with acetyl p-aminobenzoic acid in typhus infected eggs. However, an inhibitory effect on typhus rickettsiae was obtained by these authors with the heated compound due to the liberation of free PABA by hydrolysis. In our experiments only the original compound was used.

Summary and Discussion

The presented facts indicate that when PABA was given orally to guinea pigs before inoculation with a highly virulent strain of Rocky Mountain spotted fever or on the day of infection, the appearance of clinical manifestations (fever, scrotal lesions) was prevented in about 80 per cent of treated animals. The survival rate in the symptomless cases or in

animals showing abortive fevers approached almost 100 per cent as compared with 100 per cent death-rate of the untreated. The progressive delay in PABA treatment after the infection diminishes its efficiency, the 48 hours delay probably being the borderline. Once the disease has developed in the untreated animal no effect of PABA was ever observed.

The prevention of detectable clinical manifestations by PABA action does not protect the infected guinea pig from the development of pathologic lesions typical for spotted fever. This was evidenced by the finding of a large, dark and friable spleen and a frequently observed pneumonitis in afebrile and recovered guinea pigs. The transfer of the spleen from such animals into susceptible guinea pigs resulted in frank and fatal spotted fever infection. Furthermore, when the surviving afebrile animals were reinoculated with spotted fever rickettsiae they showed complete immunity. Consequently, the subclinical (symptomless or inapparent) type of infection apparently due to the suppressive rather than destructive action of PABA on the rickettsiae, conferred to the recovered guinea pigs an active immunity.

Attempts to interpret the mode of action of PABA, still in the realm of speculation, are centered around its indirect effect on rickettsiae by way of stimulation of the metabolism of the host cells. According to this working hypothesis PABA's high metabolic activity on the enzyme system is unfavorable for the multiplication of the intracellular rickettsiae. Greiff, Pinkerton and Moragues (1944) in advancing this plausible theory also consider the possibility of disappearance from the host cells of enzymes essential for rickettsial growth.

If the rather remote possibility of a direct action of PABA on the multiplication of rickettsiae can be ruled out, then it would seem that the most promising approach to the problem would be a "rational investigation of cell metabolic systems and their selective inhibition" (Mudd, 1945).

In the light of the findings submitted with the present report PABA shares the properties of many other chemotherapeutic agents "by stopping the further multiplication of

the parasites rather than by killing them outright" (Mudd, 1945). In view of its access to the intracellularly located rickettsiae, p-aminobenzoic acid is evidently provided with special potentialities of changing the metabolic processes of the host cell which inhibit the vitality of the disease agent.

Whatever the mode of action of PABA might be, large quantities of the drug are required in order to achieve a chemotherapeutic benefit in human or experimental rickettsioses. The necessity of frequent administration of the drug and the large total daily intake (up to 30 gm. in human cases) is dictated by its rapid excretion and inactivation by process of conjugation. A further inquiry into the adequate mode of administration of p-aminobenzoic acid perhaps with other adjuvants as well as the study of the significance of PABA values in the infected host are in progress in this laboratory.

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EVIDENCE ON THE INFLUENCE OF ALTITUDE ON ALLERGIC SYMPTOMS IN CHILDREN†

JULIA BAKER*

In 1944 I presented a review based on histories of 500 children in Mexico City, which indicated that allergic reactions are more common and more severe at that altitude than at lower levels. I shall here give two case histories in illustration of this fact, and thereafter a brief discussion of differences noted between the practice of pediatrics in Mexico City and that at lower levels.

Case 1. This is the history of an allergic child who was moved repeatedly between a high altitude and a lower one.

M. M. was born March 19, 1942. At the age of 4 months (July) she was first seen, at which time she had had hives twice, both times associated with loose bowel movements. Her brother and sister, also born in Mexico City, had had hives during their infancy. She had hives again in August. She then spent a month in Cuernavaca, altitude 4900 ft., 2534 ft. lower than Mexico City. She was well during this month at the lower altitude, but immediately on her return to Mexico City, on Oct. 31, she broke out in hives again, which became worse on Nov. 1. On Dec. 2, she began to have loose bowel movements, 3-6 a day, so was taken back to Cuernavaca, where this cleared up. She stayed at the lower level for six weeks. On her return to Mexico City Feb. 7, she vomited for two days. From Feb. 15 to Mar. 2 she had a running nose. On Apr. 5 she returned to Cuernavaca, remaining there until May 17, during which time she was well. On May 20, she was seen because of hives, 18 counted, and slight eczema which had developed since her return three days previously to the altitude of Mexico City. In December, she spent 10 days in Cuernavaca. On the day of her return

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to Mexico City, she developed loose bowel movements and a few hives.

The differences in her condition at 7434 ft. and 4900 ft. have not been caused by something eaten in Mexico City and not in Cuernavaca, since as a baby her diet both in Mexico City and in Cuernavaca, was Mead Johnson's Nutramigen, canned baby foods and cereals prepared in the U. S. In Mexico City, when milk products made from cow's milk and also raisins and bacon are eliminated from the diet, she continues free of major allergic symptoms. In Cuernavaca she always gains faster than in Mexico City.

Note: Since this paper was read, the following data have become available: This patient went to Los Angeles, Calif. on Dec. 5, 1945 and returned to Mexico City Feb. 7, 1946. She gained 5 lbs. during this time. She drank at least 4 cups of cow's milk daily, two of which were prepared with chocolate, and she ate ice cream nearly every day. She ate one egg a day and sometimes two. She was very well indeed for one month and three weeks. Then she developed nausea and vomiting. The treatment was enema and omission of milk and eggs for one day. She improved but never regained her former appetite, especially for eggs.

Case 2. This is the history of a child who had always been in good health before coming to Mexico City, who developed various allergic manifestations with reference to the skin, gastro-intestinal tract and upper respiratory system after arriving, who remained constantly at the high altitude, and who continued well there on the elimination of the offending foods.

A. W., born Sept. 11, 1939, was first seen Sept. 20, 1943. She had just arrived in Mexico City from Morgantown, West Virginia, where she had never had reactions to any foods. Two days after her arrival, she developed severely itching hives, 60 counted, which were located especially thick on her body. With symptomatic treatment, cleaning out of the gastro-intestinal tract and omitting those foods which most frequently cause trouble here, improvement was prompt. Omission of these foods—eggs, chocolate, orange juice, milk,

wheat—was continued for one week. Two weeks later, Oct. 13, she developed hives twelve hours after eating eggs. She lost 1.5 lbs. in the first month. On Oct. 16, she had a mild diarrhea with four loose stools a day, without fever. This responded to limiting the diet. She was not seen again until Jan. 7. By this time her mother had noted, by keeping records, that eggs had definitely caused hives on six different occasions. At this time, she had an upper respiratory condition with swollen pale inferior turbinates characteristic of allergic rhinitis. This responded to limiting the diet for a few days. On July 9, she had wheezy breathing, hives, abdominal pain, vomiting and slight fever. There was no abdominal tenderness. On July 27, she was in for a check-up and looked so thin and listless that it was decided to limit her diet for three weeks instead of the usual few days. Her food was changed from 3 cups of boiled cow's milk to ½ cup of milk a day prepared from Klim, no eggs, no chocolate, and very little wheat. Three weeks later her mother reported that she had developed a tremendous appetite, and had gained 2 lbs., more than during the preceding 7 months. It was found that milk was the major offending food. Neither this food nor any of the others mentioned had given trouble in Morgantown.

Note: Since this paper was read, the following data have become available. The child was in Ames, Iowa, from Nov. 12 to Dec. 20, 1945 where she took daily one double yolked egg and one quart of pasteurized cow's milk without reactions of any kind. She resumed her previous diet on returning to Mexico City.

Whether or not one accepts these food reactions as classical allergy, they are allergic in nature and constitute a major factor in the practice of pediatrics at this altitude. In some points they are not in accord with the classical concepts. Skin tests are usually not of great value. Ordinarily, an accumulative period can be recognized. With elimination of the offending foods for a considerable period, sensitivity is gradually lost. On resumption of those foods it builds up again, usually in a fairly constant time period. Response at

low levels may be so mild as not to become noticeable, but it becomes marked and important at the altitude of Mexico City.

In the practice of pediatrics there, in my experience, allergic reactions are as important as infections. This statement is not intended to apply to the poorer groups in the population in which infection may be high. Fifty per cent of the 500 children discussed in my paper last year had allergy severe enough to bring them to a physician. The babies begin to develop food intolerances at 7-8 months of age, usually beginning with diarrheas which give negative stool cultures, and with vomiting, and later develop allergic rhinitis and bronchitis. Urticarias and eczemas occur along with these gastro-intestinal reactions and respiratory complaints. Mothers of my patients have told me that Mexican physicians have diagnosed the skin condition as "altitude urticaria" with the statement that the babies will outgrow it. This is in agreement with the view I have expressed, that an altitude as great as that of Mexico City intensifies allergic symptoms such as urticaria, and the younger the child, after it is old enough (7-8 months) to have developed food sensitivities, the more severe the reactions. Later in life, skin conditions improve, but the children may have other allergic symptoms.

Feeding programs for infants and young children cannot follow those recommended in the United States. Eggs cannot be given every day as they are prescribed and tolerated at lower altitudes. Full caloric requirement milk formulae as given in the United States will speed up the onset of trouble. Breast fed babies in the better classes in Mexico City in my experience have an even greater advantage over artificially fed infants than that recorded in the United States, and this extra advantage is not because of freedom from infection, but because their food reactions develop later. It is not unusual, however, for a breast fed baby to be allergic to some food in the mother's diet.

Under one year, if reaction to milk develops, I have usually obtained success with one of the following: Mead Johnson's Nutramigen if the reaction is mild, burro's milk and goat's milk if the allergy is to a specific lactalbumin and not to

casein. Sobee in my experience has not been tolerated for more than three or four weeks without causing sensitivity. Milk substitute formulae have proved helpful in some cases. In other cases alternation of these different preparations has given success. After a year, a much more varied diet can be given. And in variation lies safety. The main danger seems to be from certain foods taken in large amounts or every day over a long period. As the child grows older, his severe reactions to foods become less. From 7-14 months the reactions are most severe, and may even endanger life if vomiting and diarrhea result in dehydration and chemical imbalance of the body fluids, or malnutrition predisposes to infections. By three years of age the children get along better, and by seven the reactions are much more of a chronic than an acute type.

The common contagious diseases, of course, are present in Mexico City. Except in the case of smallpox, immunization programs have not been developed to the degree seen in the United States. Whooping cough is common and severe. So also is diphtheria. Scarlet fever is common and usually mild. Poliomyelitis occurs, but only sporadically. Chicken pox and mumps occur. Typhoid fever is endemic, usually with higher frequency in the summer months. Immunization is not yet general. Bacillary dysentery is very common. Tuberculosis is common, especially in the poorer groups, and since servants take care of most of the children, they may become a source of infection. Rheumatic fever is common in charity practice. Intestinal parasites, including amoebae, are not common in the well cared for social groups, but are very common in the Children's Hospital charity clinics. In these clinics severe malnutrition and vitamin deficiencies are frequently found.

REFERENCE

Baker, Julia: A note on a possible allergic factor in altitude sickness. J. Lab. and Clin. Med., 29:831–839, 1944.

CALLING ATTENTION TO:

Items of Possible Interest to Friends of Our Effort

March, 1946

1. Symposia and Reviews: M. Shimkin opens important symposium on breast cancer with full review of experimental induction (*Surgery* 19:1–154, 1946). Note helpful symposium on sciatica, low back pain, and intervertebral disk disease by N. Little & Co. (*Med. J. Austral* 1:33–52, Jan. 12, 1946). E. H. Reinhard & Co. offer comprehensive review of radiactive phosphorus as therapeutic agent (*J. Lab. Clin. Med.* 31:107, 1946). W. Sheldon well reviews tuberculous rheumatism and H. S. Barber discusses difficulties in diagnosing rheumatic fever (*Lancet*, 119, 122, Jan. 26, 1946). Note E. W. Dempsey and G. B. Wislocki's survey of histochemistry, D. E. Gregg on coronary circulation, J. Furth on leukemia, G. H. Bishop on cutaneous sense mechanisms, A. C. Frazer on absorption of fat, J. M. Buchanan and A. B. Hastings on metabolism studies with isotope carbon, and A. P. Heusner on yawning (*Physiol. Rev.* 26:1–28–47–77–103–120–156, 1946). Watch for accumulated exuberance from March meetings Federation of American Societies for Experimental Biology (*Fed. Proc.* 5:1–1946). F. W. Bancroft and C. Pilcher edit *Surgical Treatment of the Nervous System* (Lippincott, Phila., 534 pp., 1946, $18). J. F. Fulton edits 15th ed. Howell's *Textbook of Physiology* and it's up to the minute (Saunders, Phila., 1946, 1304 pp., $8). F. Hawking and F. H. K. Green edit *The Medical Use of Sulphonamides* (Med. Res. Counc. War Memo. 10, 2nd ed., London. 1946, 71 pp., 1s 3d). B. Blanshard, C. J. Ducasse, C. W. Hendel, W. E. Murphy, and M. C. Otto survey *Philosophy in American Education* rather sourly (Harper, N. Y., 1946, 306 pp., $3). And there is still more on ethicogenesis (*Sci. Month.* 62:185, 1946).

2. Philosophical: Have you seen W. A. Sinclair's little but stimulating *Introduction to Philosophy* (Oxford Press, N. Y., 151 pp., $1.50)? L. Mumford's *The Condition of Man* is tough, tense and turgid (Harcourt Brace, N. Y., 467 pp., $5). K. Burke's *Grammar of Motives* is a semantic introduction to trilogy on human relations (Prentice-Hall, N. Y., 530 pp., $5). Mr. Cohen essays keenly *The Faith of a Liberal* (Holt, N. Y., 497 pp., $3.75). A. E. Cohn's *Minerva's Progress* emphasizes importance of dissent in tradition (Harcourt Brace, N. Y., 101 pp., $2). A. E. Clark-Kennedy discusses *Art of Medicine in Relation to Progress of Thought* (Cambridge Press, 2s, 1946).

3. Physiological: B. H. Crawford discusses photochemical principles in explanation of recovery phenomena in visual sensitivity (*Proc. Roy. Soc. B.* 133:63, 1946). A. Szent-Gyorgi discusses contraction in relation to chemical structure of muscle fibril (*J. Colloid Chem.* 1:1, 1946). T. H. Bullock & Co. report on reversible effects of inhibitors of choline esterase on nerve action potentials (*J. Neurophysiol* 9:9, 1946). Our E. Ogden pleasantly teleologizes on respiratory flow in the dogfish (*Am. J. Physiol.* 145:134, 1945). Our H. J. Ralston, W. D. Collings, A. N. Taylor and

E. Ogden find tissue elasticity helps return venous blood in absence of cardiac drive (*Am. J. Physiol.* 145:441, 1946).

4. PHARMACOLOGICAL: F. W. Schueler offers neat biochemorphic theory for sex hormonal action (*Science,* 103:220, Feb. 22, 1946). E. R. Loew & Co. find powerful anti-histamine action in triazine ethers (*J. Pharmacol. Exp. Therap.* 86:7, 1946). N. K. Schaffer and T. A. Loomis report on pyrrolidine dicarboxylic acid local anesthetics (*Yale J. Biol. Med.* 18:157–171, 1946). C. H. Andrews & Co. describe anti-rickettsial action of p-sulfonamidobenzamidine in stimulating discussion of experimental chemotherapy of typhus (*Proc. Roy. Soc. B.* 133:20–62, 1946). R. C. Gill clarifies ideas on development of curare (*Anesth.* 7:14, 1946). Watch for modified amino heptanes as vasopressors: Lilly has 2-amino heptane, now comes Bilhuber with 2-methylamino heptane (*Ibid.*, p. 62). K. Meier recommends sulfadimethylpyrimidin as best sulfa for children because of least effect on kidney (*Schweiz. Med. Woch.* 75:1097, Dec. 15, 1945).

5. ODDS AND ENDSICAL: F. C. Courtice recommends local cooling to reduce fluid loss in thermal burns (*J. Physiol.* 104:321, 1946). T. Teorell proposes quantitative theory for antigen-antibody reactions (*J. Hyg.* 44: 227–237, 1946). G. E. Burch discusses water and heat loss from lungs in tropics (*Arch. Int. Med.* 76:308–315, 1945). G. Duboff & Co. demonstrate enzyme inhibitor in serum from cancer patients (*Cancer Res.* 6:57, 1946). G. H. Twombly and D. Meisel fail to confirm A. Taylor & Co.'s idea (*Science* 97:123, 1943) of a filterable cancer virus (*Ibid.*, p. 82).

APRIL, 1946

1. FEDERATION PROCEEDINGS: From H. W. Ades on the corpus callosum to P. C. Zamecnik on lecithin and antitoxin, 1,000 plus experimental biologists abstract accumulated work of war years: symposia include human centrifuge experiments, brain metabolism, various physiological systems, synaptic mechanisms, aviation problems, nutrition, exercise, shock, and temperature regulation from physiologists; carbon metabolism, nitrogen metabolism, growth, mineral metabolism, neurospora biochemistry, isotope biochemistry, respiratory and vitamin enzymes from biochemists; diisopropyl fluorophosphate, antimalarials, anesthetics, autonomic drugs, biometrics, toxicity, chemotherapy, and cardiac drugs from pharmacologists; neoplasms, injury and repair, and hematology from pathologists; diets and world nutrition and vitamins from nutritionists, and antibiotics, viruses and immune sera from immunologists (*Fed. Proc.* 5:1–256, 1946). Silly bureaucracy prevented H. J. Curtis discussing activation of tissue elements by slow neutron exposure, even though published in abstract (*Fed. Proc.* 5:20, 1946). On what evidence did bureaucrats decide DFP (Diisopropyl fluorophosphate) is optimum of series for choline esterase inhibition? If anything could be gathered from the confusions of the meeting, it is that scientific workers are becoming more fascistic in this country. L. K. Frank suggests that scientists prepare to act as responsible accountable individuals, in asking pertinent question about obedient patriotic citizens (*Science* 103:350, March 22, 1946).

2. More New Journals: Amsterdamsche Boek—en Courant Maatschappij, Amsterdam, Holland, announces *Excerpta Medica*, an abstract journal to appear in 15 sections covering all phases of laboratory and clinical medicine, with A. P. H. A. de Kleyn, M. W. Woerdeman, and W. P. C. Zeeman as editors. Grune & Stratton, 381 4th Ave., N. Y. 16, offer bi-monthly *Blood: The Journal of Hematology*, with appropriate introductory articles on chemical components of blood by E. J. Cohn (p. 3), and primary and secondary splenic panhematopenia by C. A. Doan and C. S. Wright (p. 10). W. D. Postell reviews American contributions to the literature of geriatrics (*Geriatrics* 1:41, 1946). *Occupation Medicine* rolls along: C. P. McCord & Co. apply N. F. Maclagen's thymol turbidity test of liver dysfunction (*Brit. J. Exp. Path.* 25:234, 1944) to CCl_4 poisoning (*Occup. Med.* 1:160, 1946).

3. Reviving Pharmacology: G. A. Alles pleasantly revives worthy effort with reports on lack of advantage in depressant action of substituted phenobarbitals, and on a-methalkyl ammonium compounds (*Univ. Calif. Publ. Pharmacol.* 2:173–183, 1946). J. H. Masserman and K. S. Yum sensibly analyse influence of alcohol in experimental neuroses in cats, revealing factors in addiction (*Psychosom. Med.* 8:36, 1946). E. R. Movitt offers *Digitalis and Other Cardiotonic Drugs* (Oxford Med. Publ., N. Y., 1946). N. H. Fairley & Co. report on paludrine (M4888) in malaria (*Med. J. Austral.* 1:234, Feb. 16, 1946). Note A. Krogh's Croonian Lecture on active and passive exchange of inorganic ions through living membranes (*Proc. Roy. Soc. B.* 133:140, 1946).

4. Otherwise Interesting: Sir Henry Dale bravely condemns tendency toward scientific secrecy (*Proc. Roy. Soc. B.* 133:135, 1946). W. D. Harkins bravely discusses the neutron, the compound nucleus and the atomic bomb (*Science* 103:289, March 8, 1946). A. Huxley pauses in his retreat from reason (*Perrenial Philosopher*, N. Y., 1945) to confuse further the problems of *Science, Liberty and Peace* (Harper, N. Y., 1946, 86 pp., $1). L. Mumford reminisces toughly on *Values for Survival* (Harcourt, N. Y., 1946, 314 pp., $3). D. Masters and K. Way edit *One World or None*, designed to enlighten, maybe frighten (McGraw Hill, N. Y., 1946, $1). Philosophical Library, N. Y. 16, announce J. Dewey's *Problems of Men* to appear April 29 at $5. And the *Burma Surgeon Returns* (G. S. Seagrave, Norton, N. Y., 1946, $3).

5. Notes: M. Maizels discusses action of hemolysins on erythrocytes (*Quart. J. Exp. Physiol.* 33:183, 1946). L. Kreyberg (Oslo) reports on tissue damage due to cold (*Lancet* 1:338, March 9, 1946). Randolph Field, Texas, releases mimeographed reports from A. A. F. School Aviation Medicine of which J. S. Gray's is worthy, on multiple factor theory of respiratory regulation. In symposium on antibiotics, our M. Fulton & Co. note that penicillin has no action on alcaligenes (*Scienec* 103:361, March 22, 1946). Our G. M. Decherd and A. Ruskin discuss mechanism of A-V block (*Brit. Heart J.* 8:6, 1946).